Biology of MRONJ/Biologia della MRONJ

MEDICATION-INDUCED OSTEONECROSIS OF THE JAWS: RESEARCHING FOR NEW PROGNOSTIC BIOMARKERS FROM A MULTIDISCIPLINARY POINT OF VIEW

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Background. Medication-induced osteonecrosis of the jaws (MRONJ) is a clinically-relevant adverse effect linked to the use of anti-resorptive drugs, such as bisphosphonates, denosumab or anti-angiogenic agents.
It is currently impossible to predict whether a patient will develop MRONJ, as there is no plasma nor osseous drug concentration predicting the toxic effect of these drugs.
Moreover, even if MRONJ is often related to recurrent oral infections, research still lacks in evidence for the role of the salivary microbiome.
Therefore, this study aims at evaluating new prognostic biomarkers, through the analysis of microbiologic, drug-related and genetical aspects which could be implied in the bioavailability of these drugs, in order to predict the development of osteonecrosis.
Patients and Methods. Sixteen patients who were suffering from oncologic or metabolic bone disorders and were treated with either denosumab or zoledronate were enrolled in the study. The patients were divided into two groups: Group A consisted of eight patients who developed MRONJ, while Group B consisted of eight patients who did not develop MRONJ.
These two groups were compared by analyzing the oral microbiome through Next-Generation Sequencing, by measuring drugs' concentrations both in plasma and bone using Liquid Chromography with Tandem Mass Spectrometry, and by evaluating the presence of polymorphisms in genes influencing the metabolism or clearance of these drugs. Risk factors, including smoke and alcohol, were assessed as well.
Results. Differences were found between the two groups, with the first group having a higher usage of alcohol and a younger median age ($p = 0.003$ and $p = 0.001$, respectively). In addition, mostly of the patients who experienced MRONJ were female.
Regarding the oral microbiome, group A manifested an increase in Neisseriacee ($p = 0.049$). Concerning the dosage, group A patients were mostly administered high-dose drugs, which were both intravenously and subcutaneously injected.
Finally, the results suggested the role of polymorphism ABCB1 3435 C >T in the development of MRONJ, but with weaker impact ($p = 0.053$).
Conclusions. this study evaluates multiple aspects playing a role in MRONJ development, such as the role of the oral microbiome, drugs' concentration and genetic polymorphisms. Further studies are required to confirm these preliminary results.

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PRELIMINARY ANALYSIS OF IMMUNE SUBSETS AND PRO-INFLAMMATORY CYTOKINES IN MRONJ PATIENTS

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Background. Medication-Related Osteonecrosis of the Jaws (MRONJ) is a severe side effect observed in patients taking anti-resorptive drugs (ARDs) such as amino-bisphosphonates (N-BPs), like zoledronic acid (ZOL), and monoclonal antibodies, like denosumab (DMAB). Clinical signs of MRONJ include necrotic bone exposition and wound healing impairment; symptoms appear mostly late and the related radiographic findings may be challenging to interpret. According to current literature, the pathogenesis of MRONJ appears to be multifaceted and evidence supporting a central role of immune dysfunction consistently grew over time. To evaluate whether different ARDs could induce MRONJ through different mechanisms of action, we investigated circulating immune subsets and pro-inflammatory cytokine release. Adding insights in the pathogenesis of MRONJ is fundamental to improve the clinical management of patients undergoing treatment with such medications.

Patients and methods. In a 1-year study conducted at the Department of Oral Surgery of C.I.R. Dental School (A.O.U. Città della Salute e della Scienza, Turin, Italy) we selected 8 bone metastatic breast cancer patients, treated with ZOL or DMAB, who developed MRONJ (following diagnostic criteria proposed by the Italian Society of Maxillo-Facial Surgery and the Italian Society of Oral Medicine and Pathology, SIC-MF-SIPMO 2020). All the patients were scheduled to undergo a sequestrectomy, a type of bone resective surgery to remove necrotic bone tissue affected by MRONJ. On the day of surgery, a peripheral blood sample was obtained, peripheral blood mononuclear cells (PBMCs) were isolated and was used for an immunophenotypic analysis of some immune cell subsets ($\gamma\delta$ T cells, CD4+ T helper cells, CD8+ T cytotoxic cells, along with their activation markers CD25 and CD69) by flow cytometry. A multiplex analysis of different cytokines in sera (IL-1β, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12 (p70), IL-13, IL-17, GM-CSF, IFN-γ, MCP-1, MIP-1β, TNF-α) was performed to assess the presence of differences between the two MRONJ groups.

Results. In the group of patients with MRONJ induced by ZOL, we observed a significative higher level of CD4+ and CD8+ cells and a decreased level of CD4/CD69+ T cells compared to patients with DMAB-induced ONJ. The level of $\gamma\delta$ T cells was lower in patients who developed Zol-induced ONJ compared to patients with DMAB-induced ONJ. Significative differences also emerged by the analysis of cytokine and chemokine in sera, showing a higher level of IL-8, IL-17, MIP-1β and TNF-α in ZOL-induced MRONJ patients compared to DMAB-induced MRONJ patients.

Conclusions. The two ARDs considered revealed a different capability to modulate immune subsets and pro-inflammatory cytokines release. These preliminary data deserve further investigations since could help to identify the different regulation of immune cell subsets exerted by ZOL and DMAB, opening also new therapeutic perspectives.

EVALUATION OF THE OSTEOCLAST ASSET ASSOCIATED TO A POTENTIAL 3D-PRINTED APPROACH FOR REPAIRING BONE DEFECTS IN MRONJ PATIENTS

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Background. Medication-related osteonecrosis of the jaw (MRONJ) is a serious adverse event characterized by non-healing necrotic bone tissue of mandible or maxilla. Drugs such as bisphosphonates (BPs) and denosumab target osteoclasts, inhibiting osteoclast (OC) formation and activity, thus blocking bone resorption, without a stimulation of osteoblast (OB) activity. These anti-resorptive drugs cause the uncoupling of OC and OB activity, hindering the healing of the affected area, that are characterized by bone resorption and necrotic bone. In this study, we investigated the rate of circulating osteoclast precursors (OCP) in MRONJ patients to understand whether the local bone resorption could be linked to a more systemic dysregulation of the OC compartment. Moreover, we tested 3D-printed scaffold for biocompatibility to verify their potential use in regenerative approach.

Methods. breast cancer-induced bone metastatic patients, who developed MRONJ were enrolled in the study. Patients' PBMCs were isolated from peripheral blood samples, and cells were stained for characterization of OCPs by flow cytometry. Then, the capability of PBMCs to spontaneously differentiate into OCs in *in vitro* cultures were checked. To restore the bone damage, we tested a 3D-printed polymer/ceramic (PCL+Al2O3) scaffold to sustain the mesenchymal stem cell (ASC52hTert) growth, which could lead to regeneration of the bone tissue.

Results. MRONJ patients did not show an increased in circulating OC precursors and in *in vitro* osteoclastogenesis, as expected for the effectiveness of the anti-resorptive treatment in bone metastatic patients. The 3D printed scaffold resulted biocompatible since ASCs grew and colonized it.

Conclusions. Our results on OCPs and OCs demonstrated that in MRONJ patients there is not a systemic dysregulation of OC compartment, but the bone damage is locally controlled. Since the resorbing OC activity and the apposition of new bone by OBs are dysregulated due to the action of the anti-resorptive drugs, we investigated the potential use of a scaffold made of biocompatible materials, able to sustain the grow and the differentiation of mesenchymal stem cells, which at last could result into a repair and regeneration of the bone damage.

Imaging/Imaging

MRONJ RADIOLOGICAL FIGURES AT COMPUTED TOMOGRAPHY (CT) EVALUATION: RAD-ONJ OBSERVATIONAL STUDY. PRELIMINARY REPORT

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Background. Osteonecrosis of the jaw (ONJ), renamed Medication-Related Osteonecrosis of the jaw (MRONJ) since 2014, is a disease of recent recognition (2003), characterized by alterations that include clinical signs and symptoms (not limited to bone exposure) and simultaneous jawbone radiological destruction, better evaluated by Computed Tomography (CT) scan[1,2].

Patients and methods. We designed an observational (retrospective and prospective) study to systematically investigate the presence rate of various signs of CT semeiotics, predefined in an appropriate table (*i.e.*, focal and diffuse osteosclerosis, sequestrum, cortical disruption, periosteal reaction, osteolysis, etc.) in patients with MRONJ, diagnosed according to the criteria of the Italian SIPMO-SICMF Recommendations (2020)[2]. Data downloading utilized a user-friendly tool, REDCap (*Research Electronic Data Capture*). Patient population: patients with diagnosis of MRONJ according to Italian Recommendations SIPMO-SICMF[2], followed by Maxillofacial Unit, Oncology Unit and Hematology Unit of Alessandria Hospital. Main inclusion criteria were: clinical-radiological diagnosis of MRONJ and availability of at least one CT scan (or Cone Beam CT scan) next to MRONJ diagnosis time (within three months before or after MRONJ onset).

Results. Preliminary results: between March 2022 and December 2023, we examined data of 120 patients with MRONJ; 5 patients were considered not eligible due to lack of adequate CT images. Clinical data and radiological features of 115 patients were uploaded and are under examination. Characteristics: 41 M, 74 F; median age (at MRONJ onset) 69.6 years (Q1-Q3: 62.3-77.4). Main disease (for which patient received drug inducing MRONJ): metastatic cancer or myeloma in 91 patients (2 suffering also with osteoporosis); osteoporosis and other non-malignant disease in 24. Among cancers, 40 were breast cancer, 23 prostate cancer, 11 myeloma, 7 renal cancer, 5 lung cancer, 5 others. The treatment supposed to be related to MRONJ onset was: bisphosphonates (alone or with other agents) in 105 case, denosumab (alone or with other agents) in 23, other drugs alone (antiangiogenics: one bevacizumab, one sunitinib) in 2.

At the moment, we reviewed 160 MRONJ sites (70 patients had one MRONJ area, 30 two MRONJ sites, 10 patients three areas).

Conclusions. The sample of examined MRONJ cases appears sufficient to proceed in evaluation of radiological features and draw conclusions about the investigated issue. We are going to investigate: differences between cases related to bisphoshonates and to denosumab; differences between low dose and high dose drugs; comparison between AAOMS stage (clinical only) and SIPMO-SICMF stage (clinical-radiological staging system)[1,2].

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COMPARISON OF AAOMS STAGE AND SIPMO-SICMF STAGE IN MRONJ PATIENTS. THE EXPERIENCE OF A MULTISCIPLINARY TEAM

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Background. An American Association Oral Maxillofacial Surgery (AAOMS) task force released a definition (and a staging system) of Medication-Related Osteonecrosis of Jaw (MRONJ), based on clinical features (mainly bone exposure for at least 8 weeks, or - only after 2014 - bone to be probed through a fistula) but both definition and staging system are questioned by many experts[1]. A team supported by the Italian Societies of Oral Medicine (SIPMO) and Maxillofacial Surgery (SICMF) suggested adoption of imaging tools (mainly Computed Tomography, CT) together with clinical features[2,3] to reach diagnosis (also in suspected cases without bone exposure, classified in the so called "Stage 0" according to AAOMS) and to evaluate real disease extension.

Patients and methods. To compare the stage of MRONJ cases at the first observation time in patients receiving antiresorptive therapy (bisphosphonates, denosumab), according to two different staging systems, we reviewed charts and CT scans of patients with signs of MRONJ and a history of:

GROUP A) metastatic cancer and myeloma patients and GROUP B) osteoporosis and other non-malignant diseases.

Results. We reviewed data of 124 MRONJ patients (98 GROUP A, 26 GROUP B), observed at Alessandria Hospital by a MRONJ multidisciplinary team, with 177 MRONJ sites (80 patients with one site; 35 with two sites; 9 patients with three sites).

GROUP A: The AAOMS stage was 0/I/II/III respectively in 37/12/33/6 sites (10 not reported). The SIPMO-SICMF stage was I (involvement of only alveolar bone at CT scan)/ II (extended to extra-alveolar bone)/ III (*complicated case*) respectively in 19/64/11 sites (4 not available).

GROUP B: The AAOMS stage 0/I/II/III was respectively in 6/3/14/2 sites (1 not reported). The SIPMO-SICMF stage was I/II/III respectively in 4/15/6 sites (1 not available).

In the two groups, 58 AAOMS "stage 0" sites (with signs/symptoms and without bone exposure, formally out of AAOMS definition) were reclassified as stage I (15) or II (38) or III (5) respectively, according to SIPMO/SICMF.

Conclusions. In cancer and myeloma patients as well as in osteoporosis patients the AAOMS definition and the correlated staging system appear inadequate, potentially exposing patients to delayed diagnosis (and possibly delay of treatment planning, for example adequate surgery). The diagnosis and staging should be based not only on clinical data but also on the findings of the maxillofacial region CT scan (to be performed immediately in case of suspected disease), since the CT offers larger information about extent and severity of the disease.

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BONE SCINTIGRAPHY AND POSITRON EMISSION TOMOGRAPHY IN THE EARLY DIAGNOSIS OF MRONJ

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Background. Medication-Related OsteoNecrosis of the Jaws (MRONJ) is an adverse drug reaction characterized by the progressive destruction and necrosis of the bone in patients treated with drugs for which an increased risk of MRONJ has been described. These drugs include antiresorptive medications such as bisphosphonates and denosumab (a monoclonal antibody), but also some antiangiogenic drugs and immune modulators. Antiresorptive drugs suppress with different mechanisms the activity of osteoclasts, reducing the risks of skeletal complications in patients with bone loss. For this reason, they are used in patients affected by osteoporosis, bone metastasis from solid tumor, multiple myeloma and other conditions such as Paget's disease of bone or giant cell tumor of the bone. Antiresorptive drugs significantly reduce the risk of fracture or other bone complications for these patients, but their use is associated with the possible development of MRONJ. MRONJ is a relatively rare disease, but in oncologic patients its incidence and prevalence are higher than in the osteoporotic ones. This is due to the higher dose and different route of administrations (usually intravenous) requested for subjects affected by bone metastasis or multiple myeloma. MRONJ can also considerably reduce the quality of life of cancer patients, stressing the importance of a correct and early diagnosis for an optimum treatment. MRONJ is a clinical diagnosis based on the presence of exposed bone in the maxillofacial region of patients with current or previous treatment with ONJ-related drugs. Radiographic features of MRONJ are relatively nonspecific. However, different imaging modalities can be useful as an adjunctive aid in the diagnosis and evaluation of MRONJ patients. Among them, we can include intraoral radiographs, panoramic radiograph, computed tomography (CT), cone beam computed tomography (CBCT), magnetic resonance imaging (MRI), bone scintigraphy (BS) and positron emission tomography (PET). BS and PET are functional imaging modalities able to identify areas of altered bone metabolism through an increased tracer uptake. They can detect minimal and subclinical changes in bones, showing a high sensitivity for detecting early disease. Both techniques are widely used in oncology, especially in the diagnosis of bone metastasis and in the follow up of their treatment with antiresorptive drugs. For these reasons, cancer patients at high risk of developing MRONJ often possess BS and/or PET that may show an alteration of the jaws, thus helping in an early diagnosis of MRONJ. The aim of this study is to evaluate the effective role of bone scintigraphy and positron emission tomography in the early diagnosis of MRONJ and their possible use in the identification of patients at risk for MRONJ development.

Patients and methods. Following research in the database of "Momax" (Oral Medicine and Maxillofacial) project of the Department of Oral Sciences and Maxillofacial Surgery at "Sapienza" University of Rome, patients treated with ONJ-related drugs and who had undergone BS or PET for the evaluation of bone lesions were included in the study. The jaws of each patient were divided into 4 areas. For each area, the presence of pathological tracer uptake was evaluated and related to the eventual MRONJ development. Sensitivity, specificity and predictive values of both techniques were determined. The latency from the finding of pathological tracer uptake in BS or PET to the clinical diagnosis of MRONJ and the odds ratio were also calculated. As regards BS, the statistical significance of the sample was calculated by Yates's chi-squared test, whereas Fisher's exact test was used for PET.

Results. 31 patients with BS and 20 with PET were included in the study. Sensitivity and specificity of BS for MRONJ prediction were respectively 83.3% and 87.5%. Positive and negative predictive values were respectively 73.2% and 92.8%. The odds ratio was 35. Sensitivity of PET was 33.3%, specificity was 94.9% and positive and negative predictive values were 70.0% and 80.0%, respectively. The odds ratio was 9.333. All values were statistically significant ($p < 0.0001$ for BS and $p = 0.0025$ for PET). Median time from BS or PET positivity to clinical diagnosis of MRONJ showed a great variability for both techniques.

Conclusions. Despite some limitations, our results show that BS and PET may be accurate techniques for an early prediction of MRONJ.

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THE MEDICATION-RELATED OSTEONECROSIS OF THE JAW PITFALL: A COMPARISON OF RADIOLOGICAL FINDINGS AND SURGICAL EXPERIENCE

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Background. Medication-related osteonecrosis of the jaws (MRONJ) is an adverse drug reaction characterized by the progressive disruption and gradual necrosis of the bone tissue mainly involving the mandibular and/or maxillary bones in patients who have received antiresorptive drugs or some monoclonal antibodies with or without prior radiotherapy. Since its first reported cases in the USA in 2003, this adverse drug reaction has interested scientific and medical community worldwide, sharing experiences, medical or surgical approaches, clinical follow-up and related medicaments and their doses in order to try to understand the specific pathway involved in this unfortunate complication, find the more adequate therapy and cure or avoid this fearsome collateral damage.

Patients and methods. This retrospective study aims to highlight the difference between radiological findings and surgical experience that could represent a very common pitfall, in which medical professional could fall for MRONJ surgical approach. In our experience, we enrolled n = 25 patients, from February 2020 to July 2023, affected by MRONJ without distinction of upper or low maxilla, without limitations of dimension of affected bone tissue or specific bone region affected by MRONJ, or differences based on the specific medication and its dose. All the patients performed preoperative CT scan of the facial mass, clinical evaluation, information collection about the prior medical therapy and its doses and frequency. All the patients were classified for staging according SICMF–SIPMO 2020 recommendations outline three stages based on clinical and radiological findings. All the patients performed conservative treatment before surgical procedures. All the patients underwent surgery with a surgical planning based on the pre-operative CT scan. All the patients considered had a difference between radiological definition of healthy bone tissue and affected bone of 0,8 cm ± 2,7 cm.

Results. The concept of surgical limit compared to radiological finding could represent a misleading pitfall for the surgeon who opts to treat a patient with osteonecrosis as a matter of fact the limits of resected bone tissue were determined by intraoperative observation of bleeding margins. Our comparation was determined by measuring the dimensions of the histological sample and between the radiological sample according to the radiological margins of affected bones.

Conclusions. According to our experience, we strictly recommend to all the Head and neck surgeons who constantly try to find the most adequate and radical approach to medication-related osteonecrosis of the jaws to always aim to achieve safe and healthy margins of the affected bone, considering the vital and bleeding margins as the "correct limit" of the excision, considering that the radiological finding represent a useful but also variable esteem of the dimension of affected maxillary bone.

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DENSITOMETRY EVALUATION OF THE ORTHOPANTOMOGRAPHY OF PATIENTS WITH BISPHOSPHONATE-RELATED OSTEONECROSIS OF THE JAW

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Background. Orthopantomography as it is widely accessible, inexpensive, with a low radiation dose and comfortable for the patient, is commonly used as a first-line imaging modality. Pixel intensity analysis could be a simple and useful method to measure bone density alterations associated with BP therapy, as high bone density seen as radiographic sclerosis (whitish areas) is attributed to continued mineralization in a bone with no resorption, because of the suppressed osteoclast activity.
Objectives: To quantify jawbone mineral changes secondary to Bisphosphonate-related osteonecrosis of the jaws (BRONJ) using digital orthopantomography (OPT), and analyze the level of its clinical significance. The working hypothesis is that patients with BRONJ have higher densitometric values than those observed with the same imaging test in healthy patients.
Patients and methods. A retrospective longitudinal case-control study was carried out, that included as cases all patients diagnosed with BRONJ, regardless of route of administration of the drug, at the Central University Hospital of Asturias (HUCA). The densitometric values (DV) in OPT were analyzed using free software, comparing DV obtained between BRONJ subjects and controls, and between the osteonecrotic and non-osteonecrotic areas in the same patient, and the possible association of DV with type, dose, time and route of administration of bisphosphonate, the stage of osteonecrosis, and clinical evolution.
Results. Patients with BRONJ present higher DV than healthy patients. The magnitude of DVs depend on the osteonecrosis stage, however, it is not associated with the clinical course of the disease.
Conclusions. The orthopantomography densitometric values of BRONJ patients were significantly higher than those observed in controls regardless of the location (maxillary-mandibular-global) examined. In the mandible, it was observed that a higher evolutionary stage of the disease (Stage III) was significantly related to higher densitometric values. However, in none of the jaws, the clinical course (complete resolution / partial resolution) of the disease seems to be conditioned by densitometric parameters.

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NUCLEAR IMAGING APPLICATIONS IN PLANNING SURGICAL INTERVENTION FOR MRONJ

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Background. MRONJ (Medication related osteonecrosis of the jaws) is an uncommon but serious pharmacological adverse effect. Radiological imaging is essential for proper diagnosis and treatment planning[1]. CT (computed tomography) is the main second level examination in the diagnostic process for MRONJ, however its limits in the visualization of early stages of this pathology is often reported in literature[1, 2]. Nuclear imaging permits visualization of early bony alterations. SPECT/CT (single photon emission computed tomography/CT) has been previously employed in the evaluation of osteomyelitis, osteoradionecrosis and MRONJ [3]. Assessment usefulness and accuracy of SPECT/CT vs CT alone in preoperative diagnostic evaluation of patients with MRONJ in a single-center cohort is presented here.

Patients and methods. SPECT /CT was employed in patients diagnosed with MRONJ as second level preoperative examination. Diagnosis of MRONJ was made according to AAOMS and SICMF-SIPMO criteria. Intraindividual correlation of SPECT-CT images vs CT alone (prefusion CT images of SPECT-CT) was assessed by 2 radiologist/nuclear medicine specialist 3 oral surgeons (4-points likert scale of correspondence: 0: no correspondence, 1: underestimation, 2: overestimation, 3: full correspondence) in order to evaluate site and extension of SPECT-CT uptakes vs early & late CT signs of MRONJ.

Results. Forty-two patients (9♂,33♀, mean age 71): 29 (69%) were oncologic patients treated with high dose antiresorptive agents; 10 (24%) patients were treated with oral bisphosphonates for >5 years; 3 (7%) patients were taking low dose denosumab. Antiangiogenetic agents were associated in 3 patients (sunitinib 2, everolimus 1). Triggering factors associated were: tooth extractions (71%), sore spot (24%), periodontitis (5%). Stage according to AAOMS was 0/1/2/3 in 8/8/24/5 cases and SICMF-SIPMO was 1/2/3 in 14/26/5 cases with a clear majority of symptomatic onset of MRONJ (88.9%). SPECT-CT uptakes were always in accordance with clinical signs and symptoms and anticipated onset of MRONJ in 3 cases. Uptakes in clinically silent sites were observed in 5 cases. SPECT-CT vs CT alone intraindividual correlation revealed the underestimation of CT with regards to the alterations that could be seen in SPECT-CT in 41% cases whereas full correspondence was observed in 34 % cases.

Conclusions. SPECT-CT was found effective in evaluation of extension of MRONJ lesions vs CT alone especially in case of prevalent early unspecific signs with diffuse osteosclerotic pattern. The low specificity of nuclear imaging is debated. However, in our experience the integration of morphologic and metabolic information provided by technologic advancements seems to have improved this diagnostic tool. SPECT-CT is already employed in the stage of oncologic patients so could be a suitable option for evaluation of MRONJ lesions without an increase of biologic/economic costs for patients and health service. Its efficacy suggests possible employment also in non- oncologic patients but should be reevaluated in a greater number of cases.

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Others/Altro

THE INTEREST OF MEDICATION-RELATED OSTEONECROSIS OF THE JAW (MRONJ) ACROSS THE BIBLIOGRAPHIC UNIVERSE: A SHORT ANALYSIS

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Background. Medication Related Osteonecrosis of the Jaw (MRONJ) is a side effect of drugs administered to patients with cancer, myeloma, and non-malignant diseases (osteoporosis, rheumatic and autoimmune disorders, etc), reported since 2003. The first article about bisphosphonate-related osteonecrosis of the jaw was published in 2003 by an American maxillofacial surgeon[1], but reports rapidly increased worldwide, mostly with terms Osteonecrosis of (the) Jaw(s) (acronym ONJ) and Bisphosphonate-Related ONJ (acronym BRONJ).
Since 2014 the American Association of Oral and Maxillofacial Surgeons (AAOMS) released a position paper adopting MRONJ due to evidence of cases related to other drugs (denosumab, antiangiogenic agents, etc).
Methods. We searched in PubMed, Embase and Cochrane database. In each database we ran four independent search[2]; the keywords were, for the first: Osteonecrosis, jaw*, mandible, maxilla, all terms searched in title and abstract [tiab]; for the second: ("medication related osteonecrosis jaw"[tiab:~3]) OR ("medication related osteonecrosis jaws"[tiab:~3); for the third were (mronj) OR (mronj[tiab]) and the last were (((((("mronj"[tiab])) OR ("mronj"[all])) OR ((("medication related osteonecrosis"[all])) OR ("medication related osteonecrosis"[tiab])) AND ("jaw"[tiab])) OR ("jaw"[all])) OR ("jaws"[all])) OR ("jaw"[-tiab]))). All searches are up to 7 February 2024. We also examined Prospero repository for the ongoing reviews. We investigated the documents of patient education on MSD Manuals and Medline Plus.
Results. In PubMed the widest search, with osteonecrosis in "all fields" yielded 68902 results *versus* 1832 from the broader search in Embase (Elsevier); this big difference is maybe a bias due to the differences of the retrieval algorithm or to the efficiency of Boolean operators. One Cochrane review was published.
From 2014 to 2024, 986 articles were published. They included the official acronym "MRONJ"; in the first year 9 articles only on dentistry / maxillofacial surgery journals were published. The interest in MRONJ increased exponentially until 2021 (210 articles), it decreased in 2022 (165 articles) and grew a little in 2023 (172).
The ongoing reviews registered in Prospero data base are 64 from 2016 to 2024, including 2 Cochrane protocols.
We found a conceptual shortfall in NLM MeSH thesaurus; the NLM authority is "Bisphosphonate-Associated Osteonecrosis of the Jaw" but the bisphosphonate isn't the only cause of osteonecrosis (e.g., zoledronic acid, pamidronate, alendronate and others bisphosphonates, denosumab, sunitinib, bevacizumab and other antiangiogenic agents). The heading "Osteonecrosis", introduced in 1977, considers "medication related osteonecrosis" only as a subheading (drug therapy)[3].
In MSD manual online the MRONJ topic has been updated in March 2023 whereas in Medline Plus we found, coherently with MeSH thesaurus, only the "Bisphosphonate Therapy (and Osteonecrosis of the Jaw)" topic.
Conclusions. The bibliographic study and especially the analysis of MeSH thesaurus call attention to a disproportion of consideration between MRONJ and osteonecrosis and other bone diseases.

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WASHOUT OF BISPHOSPHONATES FROM THE JAWS AFTER PHARMACOLOGICAL TREATMENT WITH PENTOXIFYLLINE AND TOCAFEROL IN OSTEOPOROSIS PATIENTS WITH ONJ CANDIDATES FOR SURGERY

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Background and rationale of the study. Medication-related osteonecrosis of the jaws (MRONJ) is a complication related to the use of drugs in the treatment of bone oncological, metabolic diseases and bone metastases. Various therapeutic protocols have been proposed for the management of osteonecrosis, to control the disease and prevent its extension, but there is currently no unanimous consensus on which approach is the most effective. Resective surgery today is still considered the gold standard in the management of this pathology, but the high rate of recurrence makes it ineffective, and due to its demolitive character with the impossibility of associating it with reconstructive and / or rehabilitative surgery, it considerably compromises the patient quality of life, with a drastic reduction in the life expectancy of cancer patients. Hence the need to develop a therapeutic protocol capable of reducing the relapse rate and transforming the surgical approach from extremely destructive to minimally invasive. In the scientific literature no randomized controlled clinical trials exist for this purpose.

Objective and Aims. Compare the therapeutic impact of two-months pharmacological preparation with Pentoxifylline and Tocaferol in a group of ONJ subjects candidate to surgical treatment, as compared to a group undergoing preparation with placebo (sodium bicarbonate rinses).

Study Design. Prospective Randomized Controlled Clinical Trial (RCT).

Materials and methods. Inclusion criteria: Patients suffering from ONJ Stage IA (osteonecrosis extending only to the alveolar process of the jaw), taking amino-bisphosphonate (aBPs) for over 3 years for the treatment of osteoporosis. Exclusion criteria: Patients with ONJ of any stage after taking aBPs, non-aBPs, and anti-Rank-L drugs (Denosumab), in combination or not with antiangiogenics or other ONJ-related drugs for the treatment of other dysmetabolic, oncological, and metastatic bone diseases. Based on sample size calculation, it is planned to include at least 80 patients per group. After collection of demographic data, anamnesis, clinical signs of ONJ, laboratory data, CBCT imaging, all patients will initially undergo a bone biopsy with the technique of coring to obtain a bone sample to estimate the aBPs quantity using liquid chromatography. Subsequently, patients will be randomly divided into two groups using an online tool for random sequence generation: surgery after pharmacological preparation for two months with pentoxifylline and tocaferol, 600 mg x 2/day and 800 I.U. x2/day, (test group), and surgery after pharmacological preparation with placebo, *i.e.* rinses with sodium bicarbonate 1.5 g in 20 ml of physiological solution 2/day (control group). After two months for both groups, new CBCT imaging diagnostic information will be collected, and patients will undergo resective surgery, harvesting a second bone sample with coring technique, to evaluate the quantity of aBPs by liquid chromatography. The same surgeon will perform all the interventions. Patients will be recalled at 7 days, 15 days, 1, 3, 6, and 12 months, for clinical and radiographic evaluation. Any intra and post-surgical complications, any relapses, non-healing, or changes in the staging of the ONJ will be recorded. Statistical analysis will be performed to evaluate the significance of within- and between-group differences in outcomes.

Expected results. The expected results are that in the test group there will be a washout of bisphosphonates from the jaws and a significantly better clinical outcome than control group.

Conclusion and clinical relevance: This study will test the efficacy of pharmacological preparation to produce bisphosphonate washout from the jaws and will lay the groundwork for the absence of relapse, the possibility of minimally invasive surgery with the association of reconstructive and rehabilitative surgery, and therefore the formulation of a novel therapeutic protocol that could establish a new gold standard treatment.

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PATIENT ELIGIBILITY CRITERIA FOR THE SURGICAL TREATMENT OF MRONJ: INSIGHT INTO FRAILTY SYNDROME

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Medication- related osteonecrosis of the jaws (MRONJ) treatment can vary in its purpose according to clinical, psychological, and social needs of the affected patient with one constant being that the objective of treatment will always be aimed at guaranteeing the best quality of life in affected patients.

When considering treatment options for patients affected by MRONJ the oral surgeon should make the decision on the basis of the most beneficial and cost-effective strategy and this could be difficult to assess.

Patients affected with MRONJ commonly have disease circumstances which make difficult to choose between curative and palliative goals, especially when factors such as comorbidity, performance status and prognosis are taken into account.

Frailty is an important factor determining MRONJ treatment outcome therefore the tools used to assess the multidimensional aspects of frailty condition could be useful providing the oral surgeon with more data on patients' vulnerability and can be considered as a novel approach to treatment decision making.

Main intention of a multidimensional assessment of frail patients with MRONJ is identifying the medical, functional and MRONJ conditions of patients, establishing what are the treatment priorities if they are FIT, VULNERABLE or FRAIL patients choosing the treatment accordingly and developing a personalized approach based on prognosis and general conditions.

The publication of the last Italian Consensus Update 2020 on medication- related osteonecrosis of the jaws by the Italian Society of Oral Pathology and Medicine (SIPMO) summarise the good clinical practices in disease management. The experts focused among the others on the topic of MRONJ surgical therapy highlighting the issue of anticipated surgery *versus* non-surgical therapies awaiting self-sequestration.

Early surgical treatment in eligible patients is indicated even in the asymptomatic cases and increase the likelihood of long-term healing.

Nevertheless it is also important to emphasize that while treating patients with curative intent equally we also have to cure those with heavy disease burden for who radical surgical treatment may not be feasible.

Understanding frailty through validated measures such as the comprehensive geriatric assessment (CGA) and its derived Multidimensional Prognostic Index (MPI) and frailty determinants in correlation to access to intervention seems to be crucial for the diagnostic and therapeutic process of MRONJ, leading to targeted interventions with the better potential.

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