Epidemiology/Epidemiologia

MRONJ IN OSTEOPOROSIS PATIENTS *VERSUS* CANCER AND MYELOMA PATIENTS: CHANGING RATIO OVER THE YEARS IN A REGIONAL NETWORK EXPERIENCE

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Background. Medication-related osteonecrosis of the jaw (MRONJ) is mostly caused by antiresorptive agents including bisphosphonates and denosumab and/or by antiangiogenic drugs[1]. Antiresorptive agents, also known as Bone Modifying Agents (BMAs) have prescribed to: a) patients with advanced cancer disease (with bone metastases) and myeloma, mostly treated with High Dose BMAs (HD-BMA) and b) osteoporosis and other non-malignant diseases (bone, rheumatologic and autoimmune disorders), receiving Low Dose BMAs (LD-BMA)[1]. Incidence and prevalence of MRONJ in these categories of patients remain uncertain, with lack of solid epidemiologic data from large observational studies[1].

First reports of MRONJ cases were published on 2003; since 2004, some MRONJ cases were observed among patients receiving oral bisphosphonates (mostly alendronate and risedronate) but they appeared as few in first published case series, and the proportion of MRONJ cases related to osteoporosis was low (less than 10% of total cases).

Since 2005, all the oral care centers in Piedmont and Valle d'Aosta territory (4.4 million inhabitants) have collaborated to register the observed MRONJ cases, with main history and clinical features. In years 2003-2006, no MRONJ case was observed among osteoporosis patients (*versus* 156 MRONJ cases among cancer and myeloma patients treated with bisphosphonates); in the following years, MRONJ cases were observed among osteoporosis patients receiving oral bisphosphonates and/or 60 mg denosumab, with numbers growing over the years.

Patients and methods. We reviewed all MRONJ cases reported in a time span of 15 years (2007-2021) in our oral care centers among cancer/myeloma patients and among patients with osteoporosis/non-malignant diseases, to look for possible change in frequency along years.

Results. Between 2007 and 2021, we registered 892 cases of MRONJ: 176 cases among osteoporosis/LD-BMA patients (mean 11.7 cases/year) and 716 cases among HD-BMA patients (mean 59.5/year).

In 2007-2011 years, the cases were respectively 43 and 224, for a mean of 8.6 and 44.8 per year.

In 2012-2016 years, they were 68 and 256. for a mean of 13.6 and 51.2 per year.

In 2017-2021 years, they were 65 and 236, for a mean of 13 and 47.2 per year.

The mean of cases per year was stable among HD-BMA cases (with a trend towards a slight decrease), whereas it increased among LD-BMA cases (above all in the first years of the 15-year period). As a consequence, the percentage of LD-BMA related MRONJ cases in the total of observed cases increased from 15% (2007-2011) to 21% (2012-2016) to 22% (2017-2021).

Conclusions. MRONJ cases observed in the oral care centers in Piemonte and Valle d'Aosta increased in frequency over the last 15 years among patients affected by osteoporosis and non-malignant diseases, mostly treated with oral bisphosphonates and/or 60 mg denosumab. Further studies are warranted to investigate the incidence and prevalence of MRONJ in non-metastatic population undergoing LD-BMAs, as well as in advanced cancer and in myeloma patients receiving treatment including HD-BMAs, alone or together with antiangiogenic agents.

*On behalf of oral care centers of: Turin, Novara, Alessandria, Asti, Cuneo, Orbassano, Aosta, Casale Monferrato, Vercelli and others

References

1. Bedogni et al. Italian position paper (SIPMO-SICMF) on medication-related osteonecrosis of the jaw (MRONJ) Oral Dis. 2024 Feb 5. doi: 10.1111/odi.14887. Online ahead of print

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SURVIVAL DATA OF PATIENTS WITH MEDICATION-RELATED OSTEONECROSIS OF JAW (MRONJ). A MONOINSTITUTIONAL EXPERIENCE

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Background. Survival of patients with Medication-Related Osteonecrosis of Jaws (MRONJ)[1,2] is not fully explored. Survival of metastatic cancer and myeloma patients after diagnosis of bone lesions is largely variable; appropriate medical therapy (improved in last twenty years), together with antiresorptive treatment, including bisphosphonates or denosumab (Bone Modifying Agents, BMAs) can obtain prolonged survival with adequate quality of life. MRONJ is not rare in patients with bone metastatic cancer and myeloma patients, occurring mostly after prolonged BMA treatment but sometimes early (in the first 18 months of BMA treatment). Expected survival might influence the choice of BMA treatment (e.g., drug and/or duration), the perception of MRONJ risk, and even the MRONJ management.

Patients and methods. We reviewed survival data after the start of BMA treatment of MRONJ patients observed in Alessandria Hospital in 2005-2023. Jamovi software was adopted to calculate survival and draw Kaplan-Meier survival curves.

Results. We analyzed survival data of 130 patients. Main characteristics: 48 males, 82 females; median age: 66 years (95% C.I. 59-74); 86 dead, 44 alive. Underlying disease: metastatic cancer (MC group) in 88 (43 breast cancer, 24 prostate cancer, 8 renal cancer, 13 other cancers); multiple myeloma (MM group) in 14; osteoporosis and other non-malignant diseases (OP group) in 28.

Median *survival* (range) *after the start of antiresorptive treatment* was 58.3 months (95% CI 46-80) for MC patients, 177.8 months (95% CI 45-NA) for MM patients, and not yet evaluable for OP groups (28 alive; only 5 dead).

Among MC patients, median survival was 68.4 months for breast cancer patients, 55.9 months for prostate cancer patients, 28.5 months for renal cancer patients. Three- and five-year survival rates were respectively 90% and 53% (breast), 82% and 45% (prostate), 37% and 25% (renal), 76% and 60% (myeloma).

Time to MRONJ onset was 26.8 months for MC patients (95% CI 23-32); 17.1 months (95% CI 9-110) for MM patients: 70.7 months (95% CI 49-101) for OP patients; it was particularly short for renal cancer patients (median 11.3 months).

Median *survival* (range) *after MRONJ diagnosis* was: 26.1 months (95% CI 20-40) for MC patients (36 breast /32 prostate/20 renal), 144.4 months (95% CI 27-NA) for MM patients, not yet evaluable for OP patients.

Conclusions. Our data show a not short survival of MRONJ patients, even in MC and in MM patients. Data of survival support careful evaluation of short and long-term cumulative MRONJ risk (*versus* short-term absolute risk) in the choice of BMA treatment duration for bone metastatic cancer and myeloma patients.

As surgery has become the optimal MRONJ treatment (unless of deteriorated Performance Status) in recent years, exclusion of jawbone surgery due to a presumed expected short survival is not more justifiable: in most of MRONJ patients with metastatic bone cancer and myeloma, surviving for years, a surgical approach could be available, and possibly giving a better Quality of Life.

References

1. Bedogni et al. Italian position paper (SIPMO-SICMF) on medication-related osteonecrosis of the jaw (MRONJ). Oral Disease 2024 at https://doi.org/10.1111/odi.14887.
2. Fusco et al. Expected survival of cancer and myeloma patients undergoing bisphosphonates or denosumab. Potential impact on diagnosis and management of Osteonecrosis of Jaws (ONJ) Qeios 2021 at: https://www.qeios.com/read/MQ2IYG.

MEDICATION-RELATED OSTEONECROSIS OF THE JAW: CASE REPORTS BY PHARMACOVIGILANCE MONITORING IN SANTA CROCE CARLE CUNEO HOSPITAL

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Background. Medication-related osteonecrosis of the jaw (MRONJ) is a serious adverse drug reaction (ADR) that can occur during treatment with bisphosphonates and denosumab. These drugs are mainly used to reduce the risk of skeletal complications in patients with bone loss resulting from long-term cancer treatment or osteoporosis. As required by the protocol, orthopantomography, dental visit and preventive care are performed before starting treatment with bisphosphonates and denosumab.

Patients and methods. In Santa Croce Carle Hospital of Cuneo, ten cases of MRONJ were collected from 2014 to 2024 by pharmacovigilance monitoring in collaboration with the Oncology Unit. Eight patients were treated with denosumab and two with zoledronic acid. Another case of MRONJ was reported for a non-cancer patient with severe osteoporosis in treatment with denosumab. In all cases MRONJ was confirmed by clinical criteria (surgical consultation) and radiological criteria (plan radiography or CT scan).

Results. Nine patients were female. Eight of them had breast cancer: two of them were being treated with abemaciclib, one with trastuzumab deruxtecan, one with letrozole, one with eribuline, one with bevacizumab and one with everolimus and exemestane. For patients treated with denosumab MRONJ occurred after an average of 11 months and surgical treatment and/or antibiotics were used for treatment. One of these patients before the onset of MRONJ presented a submandibular purulent fistula so she was treated with antibiotics. After five months, mandibular bone exposure was observed and denosumab was interrupted.

The eighth patient was in treatment with trastuzumab and paclitaxel for breast cancer and MRONJ occurred after 8 months of treatment with zoledronic acid.

One case involved a female patient with severe osteoporosis, treated with denosumab 60 mg every six months. After about 3 years frequent dental abscesses appeared and teeth extractions was performed. Furthermore, the patient was also hospitalized for necrotic exposure of the bone and severe infection treated with antibiotics.

One case involved a male patient with kidney cancer treated with sunitinib: after 6 months of therapy with denosumab MRONJ occurred with exposure of necrotic bone associated with infection. To reduce the risk of complications, a course of antibiotics was necessary.

The last case involved a male patient with prostate cancer treated with taxanes. After about a year of treatment with zoledronic acid, MRONJ occurred with pain and bone exposure.

Conclusions. In each case reported it was necessary to stop the suspected drug. Moreover, two patients were hospitalized and underwent surgery for the ADR. Six reports have already been entered into the national pharmacovigilance network and, also according to the Important Medical Event (IME) list, these ADRs were classified as serious.

References

1. Nicolatou-Galitis O, Schiødt M, Mendes RA, Ripamonti C, Hope S, Drudge-Coates L, Niepel D, Van den Wyngaert T. Medication-related osteonecrosis of the jaw: definition and best practice for prevention, diagnosis, and treatment. Oral Surg Oral Med Oral Pathol Oral Radiol. 2019 Feb;127(2):117-135. doi:10.1016/j.oooo.2018.09.008.

REPORTING OF MRONJ CASES TO ITALIAN SYSTEM OF PHARMACOVIGILANCE (AIFA): A 18-YEAR MONOINSTITUSTIONAL EXPERIENCE

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Background. Medication Related Osteonecrosis of Jaw (MRONJ) is a side effect of drugs administered to patients with cancer, myeloma, and non-malignant diseases (osteoporosis, rheumatic and autoimmune disorders, etc.) since 2003[1].

Reporting of observed side effects of drugs is recommended by international and national authorities. "Signals" of suspected adverse reactions (not necessarily ascertained) is based on spontaneous reporting, aimed to identify unknown reactions or increase of known side effects. The WHO (World Health Organization) Program for International Drug Monitoring was established in 1968, and Italy joined it in 1975. In 1995 EMA (European Medicine Agency) was created, followed in 2001 by Eudravigilance (first European data bank for adverse drug reactions). In Italy the national Rete Nazionale di Farmacovigilanza (RNF) joined Eudravigilance in 2006.

The increase of reporting of cases of osteonecrosis of jaw related to bisphosphonates (BRONJ) induced Italian authorities in 2009 to modify the documents linked to bisphosphonates, and to release strict national recommendation[2].

After a first online platform (Vigifarmaco, 2017-2022), a new online reporting system was introduced on AIFA (Agenzia Italiana del Farmaco) website since June 2022.

In spite of a large number of MRONJ cases illustrated in papers and congresses, the reporting of MRONJ cases to the AIFA vigilance system appears insufficient to draw consistent analyses.

Patients and methods. We reviewed cases of ascertained MRONJ, reported by professional figures of Alessandria Hospital to the Italian pharmacovigilance system in 2005-2023 years.

Results. We reported to AIFA drug surveillance system 89 MRONJ cases. of confirmed MRONJ, found among patients receiving treatment including bisphosphonates and/or denosumab and/or antiangiogenics drugs. Sex: 38 M, 51 F. Median age at MRONJ diagnosis time: 69 years. Status as of January 2024:27 alive, 62 dead. Patient disease: 31 breast cancer / 22 prostate cancer / 6 myeloma / 6 renal cell cancer / 6 lung cancer / 4 other cancers / 14 osteoporosis and other non-malignant disorders.

MRONJ patients received one drug or sequence of drugs potentially inducing the side effect:

a. "low dose" bisphosphonates (alendronate, risedronate, clodronate; ibandronate for osteoporosis; yearly 5 mg zoledronic acid) and/or "low dose" denosumab (60 mg every 6 months): 14 cases;

b. "high dose" bisphosphonates (pamidronate, 4 mg zoledronic acid, ibandronate at doses for metastatic disease) and/or "high dose" denosumab (120 mg monthly): 72 cases;

c. antiangiogenic agents alone (sunitinib, bevacizumab, etc): 3 cases.

A combination of bisphosphonates and/or denosumab with antiangiogenic agents in many cancer cases.

Analyzed for reporting year: 24 in 2005-2009, 36 in 2010-2014, 21 in 2015-2019, 8 in 2020-2023.

Conclusions. Our hospital reported a mean of 5 MRONJ cases per year.

Immediate and timely reporting of MRONJ cases was not always easy (due to variable modality of diagnosis process, based on both clinical and radiological examination).

Even delayed reporting is allowed and recommended in any case (although at risk of false "clusters" of reported cases).

References

1. Bedogni et al. Italian position paper (SIPMO-SICMF) on medication-related osteonecrosis of the jaw (MRONJ). Oral Dis . 2024 Feb 5. doi: 10.1111/odi.14887. Online ahead of print.

2. Ministero della Salute: raccomandazione n.10 "Prevenzione dell'osteonecrosi della mascella/mandibola da bifosfonati" contenenti le indicazioni per la prevenzione di questo effetto indesiderato. 2009.

TIME TO MRONJ ONSET AND SURVIVAL OF CANCER AND MYELOMA PATIENTS WITH MRONJ. A REGIONAL EXPERIENCE 2005-2023

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Background. Median survival of metastatic cancer and myeloma patients after diagnosis of bone lesions is largely variable, with large range, or 25%-75% Confidence Intervals (CI). In last twenty years, innovative medical therapy obtained prolongation of expected survival of many subgroups of cancer patients with bone metastases, as well of myeloma patients, all receiving (together with backbone medical treatment) also antiresorptive treatment (Bone Modifying Agents, BMAs), including bisphosphonates and denosumab. Literature data about survival of patients developing Medication-Related Osteonecrosis of Jaws (MRONJ) are scanty[1].

Patients and methods. We reviewed survival data after the start of BMA treatment of MRONJ patients registered at hospitals of Piedmont and Aosta Valley, followed by staff of a regional cancer network (Rete Oncologica di Piemonte e Valle d'Aosta) in years 2005-2023. Inclusion criteria: metastatic cancer patients or myeloma patients, developing MRONJ after High-Dose BMAs (HD-BMAs) and followed at network centers (with known latest visit or death date). Exclusion criteria: patients with other diseases (e.g., osteoporosis and non-malignant diseases); treatment with Low-Dose BMAs (LD-BMAs); lost to follow-up or unknown death date.

A Jamovi system was adopted to calculate survival and draw Kaplan-Meier survival curves.

Results. We analyzed survival data of 827 patients. Main characteristics: 294 males, 533 females; median age: 69 years (95% C.I. 61-76); 681 dead, 146 alive at latest control. Underlying disease: metastatic cancer (MC group) in 655 (396 breast cancer, 152 prostate cancer, 21 renal cancer, 49 lung cancer, 37 other cancers); multiple myeloma (MM group) in 172. First (or only) BMA administered was zoledronic acid in 76% of patients, denosumab (120 mg) in 12%, pamidronate in 10%, other drugs in 2%.

Median survival after the start of antiresorptive treatment was 82 months (95% CI 73-89) for breast cancer patients, 53 months (95% CI 47-72) for prostate cancer patients, 77 months (95% CI 21-114) for renal cancer patients, 90 months (95% CI 80-112) for MM patients, and 34 months (95% CI 28-50) for lung cancer patients. Three- and five-year survival rates were respectively 85% and 34% (breast), 70% and 25% (prostate), 51% and 20% (renal), 88% and 39% (myeloma).

Time to MRONJ onset (median) was 36 months for breast cancer patients (95% CI 32-39); 26 months for prostate cancer patients (95% CI 23-33); 10 months for renal cancer patients (95% CI 8-47); 34 months (95% CI 25-41) for MM patients.

Median survival after MRONJ diagnosis was: 33 months (95% CI 28-36) for breast cancer patients, 21 months (95% CI 16-29) for prostate cancer patients, 29 months (95% CI 13-109) for renal cancer patients, 38 months (95% CI 29-56) for MM patients, and 13 months (95% CI 10-22) for lung cancer patients.

Conclusions. Patients with bone metastatic cancer and patients with MM developing MRONJ show a survival not necessarily short (months), with a large proportion of patients surviving at 3 and 5 years after the start of BMA treatment. Median time to onset is about 2-3 years, but it is shorter in renal cancer patients (receiving also antiangiogenic drugs). Prolonged survival after MRONJ diagnosis permits surgical treatment of MRONJ in most patients.

References

1. Fusco et al. Expected survival of cancer and myeloma patients undergoing bisphosphonates or denosumab. Potential impact on diagnosis and management of Osteonecrosis of Jaws (ONJ) Qeios 2021 at: https://www.qeios.com/read/MQ2IYG.

IMPACT OF ANTIANGIOGENIC AGENTS ON MEDICATION-RELATED OSTEONECROSIS OF THE JAW (MRONJ): A MONOINSTITUTIONAL EXPERIENCE

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Background. Medication-Related Osteonecrosis of the Jaw (MRONJ) is well known as a side effect of Bone Modifying Agents (BMAs), including bisphosphonates (BPs) and denosumab (DMB), both at "low dose" (administered mostly in patients with osteoporosis and non-malignant diseases) and at "high dose" (principally in patients with bone metastases of solid cancer and in myeloma patients)[1].

MRONJ was initially reported only in metastatic bone cancer and multiple myeloma patients receiving intravenous BPs, but reports quickly included osteoporosis patients treated with oral BPs and finally patients receiving DMB and several biological agents[2].

Since 2009, the use of antiangiogenic agents (AAs) alone or in combination with BMAs has been linked to MRONJ occurrence in different patient populations. AAs reported as involved in cases of MRONJ include: anti-vascular endothelial growth factors (VEGF) drugs, tyrosine-kinase inhibitors (TKIs), mammalian target of rapamycin (m-TOR) inhibitors[2].

However, literature is scarce about the number of MRONJ cases receiving AAs, as most of the papers are case reports and case series with few patients. Impact of AAs on the total of MRONJ cases and risk estimates of MRONJ due to AAs cannot be drawn from isolated case reports and limited case series.

Patients and methods. We investigated administration of agents with antiangiogenic activity among 89 MRONJ cases observed at Alessandria Hospital between 2005 and 2023 in patients with metastatic solid cancer (breast, colorectal, renal, thyroid, lung, ovary cancer); myeloma was excluded by this analysis. We looked for use of:

a. anti VEGF agents (bevacizumab, aflibercept);
b. tyrosine kinase inhibitors (sunitinib, sorafenib, pazopanib, lenvatinib, etc.);
c. mTOR inhibitors (everolimus).

Results. Out of 89 MRONJ cases, we found 16 patients (18%) that have received AAs:

- 8 renal cancer patients: 1 treated with sunitinib alone (without bone metastases); 1 treated with sunitinib for years and later also with denosumab; 6 with bone metastases, receiving BMAs (zoledronic acid or denosumab) due to bone metastases and several AA agents (mostly sunitinib, pazopanib, everolimus) as systemic cancer treatment (usually for more lines);
- 4 breast cancer patients with bone metastases, receiving BMAs (zoledronic acid/denosumab) and bevacizumab together with chemotherapy;
- 2 colorectal cancer patients: 1 without bone metastases and developing MRONJ due to bevacizumab, 1 with bone metastases receiving DNB and bevacizumab plus aflibercept;
- 1 patient with ovary cancer receiving bevacizumab together with chemotherapy (without BMAs);
- 1 patient with bone metastases from thyroid cancer, treated with zoledronic acid and lenvatinib.

Conclusions. The possible impact of AAs on the MRONJ global occurrence in the metastatic cancer population is not irrelevant.

We observed both MRONJ cases due to AA alone (4) and MRONJ cases in which AAs could have increased the MRONJ risk due to BMAs (12).

Estimates of MRONJ risk due to AAs are to be drawn by analysis of large patient populations treated with BMAs and/or AAs.

References

1. Bedogni et al Italian position paper (SIPMO-SICMF) on medication-related osteonecrosis of the jaw (MRONJ). Oral Disease 2024 at https://doi.org/10.1111/odi.14887.

2. Fusco et al. Expert Opin Drug Saf. 2016 Jul;15(7):925-35. doi: 10.1080/14740338.2016.1177021.

Clinical aspects and case series/
Aspetti clinici ed esperienze di casistiche

CLINICAL, RADIOLOGIC AND TREATMENT FEATURES OF PERI-IMPLANTITIS INDUCED MEDICATION RELATED OSTEONECROSIS OF THE JAW: A CASE SERIES

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Background. Medication-related osteonecrosis of the jaw (MRONJ) is a pathologic condition of the maxillary bones arising following the treatment with anti-resorptive/antiangiogenic drugs for the modulation of bone remodeling. MRONJ is currently defined by the clinical presence of exposed bone or bone that can be probed through an intraoral or extraoral fistula(e) for more than 8 weeks, with an history of administration of antiresorptive or antiangiogenic agents, in the absence of previous head and neck radiation therapy or jaw metastases of other tumors. While the available literature has highlighted a strong correlation between tooth extraction and MRONJ onset, data on the relationship between dental implants and MRONJ are still controversial. The aim of the present study is to report a case series of patients with peri-implantitis induced medication-related osteonecrosis of the jaw, describing the clinical and radiologic features of the condition and the surgical treatment outcome.

Patients and methods. Thirty-six consecutive patients with clinical diagnosis of peri-implantitis associated with MRONJ were retrospectively included in the study. The sample was stratified depending on oral, pharmacological, and general health variables. The number of affected implants was recorded in all patients, and MRONJ staging applied. Surgical treatment was performed with a standardized operative protocol, involving implant removal, sequestrectomy, debridement of soft tissue, and bone curettage. Follow-up was performed at 12 months after surgery.

Results. Patients were almost equally distributed in terms of underlying diseases between osteoporotic and oncologic patients. All MRONJ lesions were symptomatic, and in 15 patients bone exposure was detected. In total, 123 implants were evaluated, with MRONJ being present around 68 implants. Twenty-four patients were diagnosed with Stage III MRONJ, and twelve patients with Stage II MRONJ. Surgical treatment leaded to complete healing in 84.4% of cases, with 100% success for maxillary MRONJ.

Conclusions. The clinical signs of peri-implantitis may reveal the presence of an underlying MRONJ diagnosis in patients under pharmacological treatment with anti-resorptive/antiangiogenic drugs. Surgical treatment seems to have a positive impact on MRONJ treatment in cases of peri-implant involvement. However, monitoring and prevention are fundamental in patients under pharmacological treatment with anti-resorptive/antiangiogenic drugs, as peri-implant MRONJ can develop also in absence of specific traumatic events.

References

1. Nisi M, Izzetti R, Gennai S, Bellini P, Graziani F, Gabriele M. Surgical Management of Medication-Related Osteonecrosis of the Jaw Patients Related to Dental Implants. J Craniofac Surg. 2020 Jun;31(4):1037-1041.
2. Tempesta A, Capodiferro S, Mauceri R, Lauritano D, Maiorano E, Favia G, Limongelli L. Peri-implantitis-like medication-related osteonecrosis of the jaw: Clinical considerations and histological evaluation with confocal laser scanning microscope. Oral Dis. 2022 Sep;28(6):1603-1609.

MEDICATION-RELATED OSTEONECROSIS OF JAWS (MRONJ) IN METASTATIC COLORECTAL CANCER: IS IT RARE? A REGIONAL EXPERIENCE WITH 10 CASES

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Background. Medication-Related Osteonecrosis of the Jaw (MRONJ) has been reported in patients treated with bisphosphonates since 2003 and was later observed not only after treatment with Bone Modifying Agents (BMAs), including bisphosphonates and denosumab, but also after antiangiogenic agents (AAs) alone, such as bevacizumab, aflibercept, sunitinib, etc. (without BMA therapy)[1-3]. MRONJ was defined by AAOMS (American Association of Oral Maxillofacial Surgeons) as the presence of exposed, necrotic bone in the maxillofacial region (or oral fistula, since 2014) that has persisted for more than eight weeks in patients with current or previous treatment with BMAs and/or AAs, and no history of head and neck radiation to the jaws; however, the occurrence of cases without bone exposure questioned that definition[1].

Patients with Metastatic Colorectal Cancer (mCRC) usually receive treatment with chemotherapy, often together with biological agents (including AAs). Bone involvement in mCRC patients is often associated with higher disease burden, worse prognosis, impaired quality of life, and significant health-related cost[2]. Bone metastases were relatively rare in the "fluorouracil era" (till the 1980s) and slightly increased in frequency after introduction of other chemotherapy drugs and of biological agents (e.g. drugs with anti-VEGF activity, and other agents) possibly reflecting the improvement in overall survival[2].

MRONJ has been reported:

a) in mCRC patients with bone metastases receiving BMAs as supportive care therapy (with/without administration of AAs within their systemic treatment);

b) in mCRC patients without bone metastases, receiving anti-VEGF without BMAs.

Patients and methods. To investigate frequency and characteristics of MRONJ in mCRC patients, we reviewed all MRONJ cases reported in 2006-2023 years in oncology and oral care centres of Piedmont and Valle d'Aosta.

Results. We registered 10 cases of MRONJ among 892 cases of MRONJ in cancer and myeloma patients (0.1% of the total number of cases). Characteristics: 8 M, 2 F; median age 65 years (range 40-78). Status at December 2023: 2 alive, 8 dead.

MRONJ-related treatment:

a. in 6 patients: BMAs (4 zoledronic acid, 2 denosumab) with/without AAs (bevacizumab / aflibercept);

b. in 4 patients: AAs alone (3 bevacizumab, 1 aflibercept).

Median survival from the start of treatment (BMA and/or AA) was 33 months (with a large range: 6-170 months).

Median survival after MRONJ diagnosis was 11 months (range 3-120).

Conclusions. MRONJ in mCRC patients is not frequent, but the chance of MRONJ has to be kept in mind by oncologists and dental professionals in patients receiving treatment for mCRC. MRONJ occurrence in mCRC patients appears low and MRONJ seems to occur in subjects with longer survival than media; however, analysis of other data (including large patient population not developing MRONJ – as control) is needed.

References

1. Bedogni et al. Italian Position Paper (SIPMO-SICMF) on Medication-Related Osteonecrosis of the Jaw (MRONJ). Qeios 2023 at www.qeios.com/read/PBUJ6Z.

2. Dell'Aquila et al. Bone metastases are associated with worse prognosis in patients affected by metastatic colorectal cancer treated with doublet or triplet chemotherapy plus bevacizumab: a subanalysis of the TRIBE and TRIBE2 trials. ESMO Open 2022 at https://doi-org.bvsp.idm.oclc.org/10.1016/j.esmoop.2022.100606.

3. Erovigni et al. Delayed Diagnosis of Osteonecrosis of the Jaw (ONJ) Associated with Bevacizumab Therapy in Colorectal Cancer Patients: Report of Two Cases. Dentistry Journal 2016 at https://doi-org.bvsp.idm.oclc.org/10.3390/dj4040039.

MRONJ: DENOSUMAB ROLE IN CANCER PATIENTS. A REGIONAL NETWORK EXPERIENCE

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Background. Denosumab (DMAb) is a human monoclonal antibody that binds and inhibits RANKL, a potent cytokine that stimulates osteoclast differentiation, proliferation and action. DMAb is considered a relevant option in the treatment of osteoporosis and bone metastases. Its mechanism of action is remarkably different from bisphosphonates (BPs) because it has no affinity for bone mineral.

Literature data show that the DMAb is potentially more active and more comfortable (subcutaneous injection) than zoledronic acid, but DMAb-related risk for MRONJ is slightly higher than that one after zoledronic acid, at least at short term evaluation (2-3 years)[1].

The aim of this work is to examine retrospectively the Medication-Related Osteonecrosis of the Jaw (MRONJ) cases observed at main hospitals in Piedmont and Valle D'Aosta territory, looking for the role of DMAb (administered at dose of 120 mg every 4 weeks) in patients with solid cancer and bone metastases.

Patients and methods. Data were retrospectively collected from different hospitals of two regions in a time spam of 9 years (from January 2014 to December 2022). We examined; sex, age at the time of diagnosis of ONJ, main disease for which DMAb and other drugs were prescribed, and type of treatment received.

Results. Data of 395 patients with MRONJ were collected, of which 265 were female and 130 were male.

Regarding the treatment received:

- 96 (24%) patients were treated with DMAb alone;
- 2 (1%) with DMAb and an antiangiogenetic agent;
- 40 (10%) patients had been switched from BPs to DMAb treatment (39 patients received zoledronate as first therapy; 1 patient received risedronate and then DMAb);
- the remaining 257 patients (65%) were treated with BPs and/or antiangiogenetic agents without DMAb treatment.

Evaluating the sample who received DMAb only, 66 patients were female and 30 were male. The average age at diagnosis of MRONJ was 66 years (SD 11.43; range 42-86) for females and 72 years (SD 9.8; range 50-88) for males. Underlying disease was reported as breast cancer in 60 (63%) patients, prostate cancer in 19 (20%), lung cancer in 8 (8%), renal cancer in 4 (4%) and other tumors in 5 (5%).

Conclusions. DMAb has become a diffuse alternative to BPs (zoledronic acid) in supportive care of patients with bone metastases from solid cancers.

Furthermore, many patients were switched from BPs to DMAb after introduction of DMAb in Europe (in 2011).

As in other reports[2], we registered a relevant number of MRONJ cases in patients receiving DMAb as front-line treatment and in patients switched from zoledronic acid to DMAb.

However, studies of large populations treated with/without DMAb (developing and not developing MRONJ) are needed to ascertain the MRONJ risk related to several treatment types, along years.

*On behalf of oral care centers of: Turin, Novara, Alessandria, Asti, Cuneo, Orbassano, Aosta, Casale Monferrato, Vercelli

References

1. Bedogni et al Italian position paper (SIPMO-SICMF) on medication-related osteonecrosis of the jaw (MRONJ). Oral Disease 2024 at: https://doi.org/10.1111/odi.14887.

2. Loyson et al Incidence of osteonecrosis of the jaw in patients with bone metastases treated sequentially with bisphosphonates and denosumab. Acta Clin Belg. 2018 Apr;73(2):100-109. At: https://doi.org/10.1080/17843286.2017.1348001.

MEDICATION-RELATED OSTEONECROSIS OF THE JAWS: A RETROSPECTIVE SINGLE CENTER STUDY

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Background. Medication-related osteonecrosis of the jaw (MRONJ) is a serious side effect of antiresorptive or antiangiogenic therapies. Controversy remains regarding the best treatment practices for the management of patients with MRONJ. The purpose of this research project is to describe and assess the characteristics, the risk factors, the diagnosis, the management, and outcomes of MRONJ in a single third level center.

Patients and methods. This study is based on a systematic computer-assisted database that allows to record patients with MRONJ in a single University third level center, since January 1st 2010 to today.

The medical charts were analyzed and the following data were recorded for each patient: gender, age, voluptuary habits, comorbidities, drugs, diagnosis, treatment, outcome.

Results. A total of 54 patients (32 females, 22 males) were included in this study, with a mean age of 59,8 years at diagnosis. Of these, 50 patients had received antiresorptive or antiangiogenic therapies because of cancer, while 4 patients were diagnosed MRONJ following osteoporosis medications. The most frequently observed cancer was multiple myeloma (17 patients), followed by breast cancer (13 patients), and prostate adenocarcinoma (5 patients)- The most frequently involved medication was zoledronate (33 patients), followed by pamidronate (5 patients), and alendronate (4 cases). The most important local risk factor for MRONJ was a tooth extraction in 28 cases. Mandible was involved in 28 cases and maxilla in 15 cases, whereas both were involved in 11 cases. Twenty-two patients underwent surgical treatment, mainly by sequestrectomy or debridement.

Conclusions. Although it occurs with high frequency and is harmful, the exact mechanism of MRONJ remains unknown, and systematic and targeted approaches are still lacking. Dental practitioners and oral surgeons focus on the etiology of osteonecrosis in the mandible and maxilla as well as the appropriate oral interventions for high-risk patients. Adequate nursing care and pharmacotherapy management are crucial too.

References

1. Coropciuc R, Moreno-Rabié C, De Vos W, Van de Casteele E, Marks L, Lenaerts V, Coppejans E, Lenssen O, Coopman R, Walschap J, Nadjmi N, Jacobs R, Politis C, Van den Wyngaert T. Navigating the complexities and controversies of medication-related osteonecrosis of the jaw (MRONJ): a critical update and consensus statement. Acta Chir Belg. 2023 Dec 7:1-11.
2. Liu C, Xiong YT, Zhu T, Liu W, Tang W, Zeng W. Management of Tooth Extraction in Patients Taking Antiresorptive Drugs: An Evidence Mapping Review and Meta-Analysis. J Clin Med. 2022 Dec 28;12(1):239.
3. Kuehn S, Scariot R, Elsalanty M. Medication-Related Osteonecrosis: Why the Jawbone? Dent J (Basel). 2023 Apr 23;11(5):109.

REPORT OF 74 MRONJ CASES OVER 5-YEARS OBSERVATION, 2019-2023

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Aim. Report of the ONJ cases that accessed to the Dental School of Brixia from January 2019 to December 2023.

Methods. After a retrospective research and analysis of each of the 74 cases of ONJ, a specific dataset has been compiled recording drug and period of taking, pathology, cause of ONJ, treatment, staging and recurrence of ONJs.

Results. According to the literature, the 64,9% of the ONJs were seen in women and 35,1% in men. The drugs involved, in order of highest risk of MRONJ, were: zoledronic acid (37,8%), denosumab 120 mg-monthly (31,1%), alendronic acid (18,9%), denosumab 60 mg-half yearly (6,8%), ibandronic acid (2,7%), unknown (2,7%). In particular, the drugs were so distributed: the 33% of women took denosumab 120 mg-monthly, followed by 25% zoledronic acid and 25% alendronic acid, while the 62% of men took zoledronic acid, followed by 27% denosumab 120 mg-monthly and 8% alendronic acid.

The drugs were prescribed for: multiple myeloma (23%), carcinoma (50%) and osteoporosis (27%).

The causes of ONJ observed were: 35% decubitus, 32% tooth extractions, 12% periimplantitis followed by spontaneous (8%) and periodontal disease (6%).

ONJs were divided in different stages: I, II, III. The stage was analyzed in relation to the drug taken: according to the literature, the highest stage (III observed in 31% of the ONJs) was related to the assumption of zoledronic acid and denosumab 120-monthly. Both of them were also involved in stages I-II (in higher percentages), while denosumab 60 mg-half year determined only 6,8% of the ONJs, at stages I-II (low entity ONJs). Alendronic acid was related to all stages.

53% of the ONJs were observed in patients still under antiresorptive treatment at the moment of the diagnosis, while the 30% had stopped treatment since less than one year. Most of them (50%) assumed the treatment for 1-5years (of which 49% zoledronic acid, 32% denosumab 120-monthly, 11% denosumab 60-half year and 8% alendronic acid). In addition to this, 16% of the patients took the treatment for more than 10 years (mostly alendronic acid), 11% for 1 year or less (mostly zoledronic acid) and 8% for 5-10 years (mostly zoledronic acid). It was impossible to detect the treatment duration in 15% of the patients (mostly denosumab 120mg-monthly).

For statistical analysis, ONJ's treatments were divided into conservative and surgical: surgical treatment (39%), medical therapy with periodic controls (8%), only periodic controls (12%), maxillofacial surgery (28%), hyperbaric chamber (4%). 5% of the patients did not undergo any treatment because of their systemic conditions.

We detected also 12% ONJ recurrences of local and maxillofacial surgical treatment.

3 cases out of 74 were patients followed by us throughout the primary and secondary prevention phase, while all the other cases are referred patients.

Conclusions. The data are consistent with the incidences found in the literature. We consider it possible to reduce the ONJ event in patients under denosumab 60mg-half yearly treatment with a correct drug modulation. It is also possible to minimize the decubitus percentage with a correct follow up of the edentulous patient.

From our experience, a better management of ONJ cases is allowed by a constant and close collaboration with the maxillofacial department.

References

1. Campisi G, Bedogni A, Fusco V. "Raccomandazioni clinico-terapeutiche sull'osteonecrosi delle ossa mascellari (ONJ) farmaco-relata e sua prevenzione" (Versione 2.0; Luglio 2020).
2. Mensi M, Audino E, Scotti E et al. "MRONJ: comparison between two surgical approaches". Dental Cadmos. 2021; 89(02):130.

PREVENTION, SCREENING AND DIAGNOSIS OF MRONJ: UPDATE OF MULTIDISCIPLINARY EXPERIENCE AT ALESSANDRIA HOSPITAL

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Background. Patients at risk of Medication-Related Osteonecrosis of the Jaw (MRONJ) include mostly cancer and myeloma patients receiving antiresorptive treatments (bisphosphonates or denosumab) with/without biological agents, but also patients with osteoporosis and other non-malignant diseases[1]. Since 2006, a MRONJ Multidisciplinary Team has been established in Alessandria Hospital, including: maxillofacial surgeons /dentists, oncologists, hematologists, nurses, radiologists, nuclear medicine and other medicine specialists, data managers[1]. So called "preventive" measures (aimed at risk reduction) before antiresorptive treatment (*i.e.*, dental visit; dental panoramic Rx; if needed: teeth extractions, dental care, and denture care) and during therapy have been planned, according to national recommendations[2]. Furthermore, other patients received care at our centre if: a) MRONJ was suspected after treatment for cancer and myeloma in neighboring hospitals, or b) MRONJ was suspected among osteoporosis patients in the provincial territory by private practice dentists or physicians.

Patients and methods. We updated our data, published on 2021[3], about more than 900 patients observed by members of the MRONJ Team, analyzing characteristics of cases confirmed as MRONJ according to Italian (SIPMO-SICMF) definition and recommendations[2].

Results. We followed 130 cases of confirmed MRONJ, found among patients receiving treatment with bisphosphonates and/or denosumab and/or antiangiogenics drugs, after both clinical and imaging evaluation. Second-level imaging was mostly based on Computed Tomography (CT scan) and occasionally included PET-TC or nuclear medicine exams (bone scan and/or SPECT). Sex: 48 M, 82 F. Median age at MRONJ diagnosis time: 69 years (range 45-90). Status at January 2024: 45 alive, 85 dead.

Patient disease: 43 (33.1%) breast cancer / 24 (18.4%) prostate cancer / 14 (10.7%) myeloma / 8 (6.1%) renal cell cancer / 6 (4.6%) lung cancer / 7 (5.4%) other cancers / 28 (21.5%) osteoporosis and other non malignant disorders.

The only drug involved in the MRONJ development was: zoledronic acid in 56, denosumab (monthly 120 mg) in 18, denosumab (60 mg every 6 months) in 4, pamidronate in 9, ibandronate (several dosages and schedules) in 6, alendronate in 9, antiangiogenics alone in 4 (2 bevacizumab, 2 sunitinib). Drug sequences of bisphosphonates, with/out denosumab (high or low dose), were reported in remaining cases.

Conclusions. In recent years we observed a slight increase of MRONJ cases observed in:

a. patients with osteoporosis and other non- malignant diseases (*i.e.*, rheumatic, autoimmune, etc.), mostly receiving "low dose" bisphosphonates and/or "low dose" denosumab (60 mg every 6 months), and

b. patients receiving denosumab, both at "high dose" (120 mg) and "low dose" (60 mg).

Even if the individual risk is very different along their drug history (5-20% for metastatic cancer patients and myeloma patients, with higher values in long survivors, *versus* less than 1% in patients receiving "low dose" drugs), the large number of osteoporosis patients treated for several years justifies the observed increase.

References

1. Bedogni et al Italian position paper (SIPMO-SICMF) on medication-related osteonecrosis of the jaw (MRONJ). Oral Diseases 2024 at: https://doi.org/10.1111/odi.14887.

2. Campisi et al. Raccomandazioni clinico-terapeutiche sull'osteonecrosi delle ossa mascellari (ONJ) farmaco-relata e sua prevenzione at: https://www.sipmo.it/wp-content/uploads/2020/08/SICMF-SIPMO-2.0_web-con-cover-2020.pdf.

3. Fasciolo et al Prevention and screening of Osteonecrosis of Jaw (ONJ): the Alessandria experience of a multidisciplinary team on a 900-patient population. Qeios https://www.qeios.com/read/0QK8E2.

DENTAL IMPLANT TREATMENT AND ONJ

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Background. Medication related osteonecrosis is the most recently described nosological entity in dentistry. The first reports are from 2003 while the first classifications are from 2007. At the beginning, the pathology was related to bisphosphonates BRONJ. Currently, it is related to many other pharmacological classes therefore called MRONJ or just ONJ. There is a fundamental division between osteometabolic (low dose, LD) and oncological (high dose, HD) patients. In addition to the aforementioned bisphosphonates, other drugs are involved in the pathological phenomenon: RANK ligand inhibitors, antiangiogenics, tyrosine kinase inhibitors, immunomodulators, and biological target drugs. According to many authors, the prevalence of ONJ is under-reported in Italy[1]. Recently, the complete digitization of the AIFA adverse occurrence report form has made the procedure immediate. Implantology is a risk factor even because of the epithelial violation, than surgical procedures. Two profiles related to ONJ associated with implantology are then outlined: the presence of implants as a risk factor for ONJ or implant surgery as a risk factor[2]. Some guidelines and recommendations are available such as SIOMMMS of 2016, which report a total of 12 cases described of spontaneous ONJ associated with implants, with a risk of implant loss of 0.88% (therefore substantially lower than that reported in the patient not on therapy), also claiming that "there is no contraindication to perform implants during BF therapy"[3]. The SIPMO/SICMF Recommendations of 2020 are of a different advise, according to which, under certain conditions, in LD patients, implant treatment cannot be excluded. However, they argue that there is a long-term risk that cannot be assessed. Another international document is the AAOMS consensus update of 2022, which converges with the Italian recommendations.
Aim of the study is to report a series of patients with ONJ associated with endosseous implants.

Patients and methods. A literature review was carried out to understand the pathology. Consecutive patients who had access to our department, who were diagnosed with spontaneous ONJ on endosseous implants according to the SIPMO/SICMF 2.0 criteria, were collected.

Results. 16 patients were collected: 9 LD patients (5 patients stage 1, 3 patients stage 2 and 2 patients stage 3; 7 alendronate and 2 denosumab) and 7 HD patients (4 patients stage 1, 2 patients stage 2 and 1 patient stage 3; 5 multiple myeloma and 2 breast cancer; 4 zoledronate, 2 denosumab and 1 imatinib). The most frequent site was the mandible in both LD patients (7 out of 9 cases) and HD patients (5 out of 7 cases). One LD patient had bimaxillary ONJ. The most frequent sex was female in LD patients (9 out of 9 cases) and male in HD patients (4 out of 7 cases). The total number of implants involved was 29 (19 in LD patients and 10 in HD patients).

Conclusions. The risk of spontaneous ONJ associated osseointegrated endosseous implants is rare, however, with an underestimated prevalence. The long-term risk of ONJ appears to be un-assessable, according to SIPMO/SICMF and AAOMS.
It is mandatory to perform a correct anamnesis and furthermore to report any osteonecrosis to AIFA. In the future, it would be useful to correlate, even with multicenter studies, given the prevalence, the drug used and the implant morphology, specifying the surface and/or the connection.

References

1. Otto S et al., Osteoporosis and bisphosphonates-related osteonecrosis of the jaw: not just a sporadic coincidence--a multi-centre study. J Craniomaxillofac Surg. 2011 Jun;39(4):272-7.
2. Giovannacci I et al., Medication-Related Osteonecrosis of the Jaw Around Dental Implants: Implant Surgery-Triggered or Implant Presence-Triggered Osteonecrosis? J Craniofac Surg. 2016 May;27(3): 697-701.
3. Rossini M et al., Guidelines for the diagnosis, prevention and management of osteoporosis. Reumatismo. 2016 Jun 23;68(1):1-39.

THE GROWING IMPORTANCE OF PERIMPLANTITIS AS LOCAL RISK FACTOR OF MRONJ. THE EXPERIENCE OF MAURIZIANO ORAL SURGERY UNIT 2015-2023

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Background. MRONJ (medication related osteonecrosis of jaws) is an uncommon adverse effect which is known to be commonly triggered by oral surgery interventions, odontogenic infections (chronic apical periodontitis, periodontitis) as well as sore spot in patients wearing removable dentures[1]. With the outspread of dental implantology in the last three decades an increased number of edentulous patients could be rehabilitated with this modality. Perimplantitis is an inflammatory condition of perimplant surrounding tissues whose mean prevalence reach 22%[2]. In last years, cases of implant related MRONJ have been documented. However, whether the implant insertion or subsequent development of perimplantitis is the main trigger of MRONJ is a matter of debate[3]. A retrospective evaluation of MRONJ cases treated in our center from 2016 to 2023 is presented here.

Patients and methods. Data from hospital records regarding patients diagnosed with implant triggered MRONJ were retrospectively retrieved. Implant triggered MRONJ was defined as subsequent MRONJ following implant insertion or perimplantitis. Number of implants triggered MRONJ was later compared with total cases of MRONJ observed in our institution in the same period. Diagnosis of MRONJ followed AAOMS and SICMF-SIPMO criteria.

Results. One hundred and one patients were diagnosed of MRONJ in our institution from 2015 to 2023. Among them 9 (9%; M/F: 3/6, mean age: 68 years) patients developed MRONJ around dental implants. Drugs related were oral bisphosphonates (4), intravenous bisphosphonates (5), denosumab high dose (1), denosumab low dose (2), one patient which took oral bisphosphonates later shifted to denosumab low dose. Site of MRONJ was: maxilla (2), mandible (7). Classification according to AAOMS was 0/1/2/3 in 1/1/5/3 and SICMF-SIPMO was 1/2/3 in 4/2/3. Eight patients developed MRONJ because of perimplantitis (time range after implant insertion 3-10 years), in one case the osteonecrosis developed soon after implant insertion. All patients underwent conservative resective surgery under general anesthesia with definitive resolution in 7 patients. Two patients underwent surgical reintervention because of MRONJ recurrence. One patient had a mandibular pathological fracture fixed with osteosynthesis plates.

Conclusions. Correlation between MRONJ antiresorptive drugs employed for bone metastasis in cancer treatment is well documented and lead to severe restrictions to implant therapy. Otherwise about 30 million people were in therapy with antriresorptive drugs in 2015 for osteometabolic reasons. In this case limitations to implantology are not clearly defined since the unpredictability of risk of development of MRONJ[3]. However considering the greater number of patients exposed to these medications, the greater proportion of patients treated with low dose denosumab and ageing of people (which correlates with higher comorbidities, edentulism but also perimplantitis), the risk-benefit assessment should consider carefully the possible development of MRONJ surrounding dental implants over time.

References

1. Bedogni A., Campisi G., Fusco V. Raccomandazioni clinico-terapeutiche sull'osteonecrosi delle ossa mascellari (ONJ) farmaco-relata e sua prevenzione versione SICMF-SIMPO 2.0 03/2020.
2. Roccuzzo, A.; Stähli, A.; Monje, A.; Sculean, A.; Salvi, G.E. Peri-Implantitis: A Clinical Update on Prevalence and Surgical Treatment Outcomes. J. Clin. Med. 2021, 10, 1107. https://doi.org/10.3390/jcm10051107.
3. Stavropoulos A, Bertl K, Pietschmann P, Pandis N, Schiødt M, Klinge B. The effect of antiresorptive drugs on implant therapy: Systematic review and meta-analysis. Clin Oral Implants Res. 2018 Oct;29 Suppl 18:54-92.

Non-malignant diseases (osteoporosis, CTIBL)/
Patologie non maligne (osteoporosi, CTIBL)

MRONJ IN PATIENTS WITH OSTEOPOROSIS AND NON-MALIGNANT DISEASES: 184 CASES IN A REGIONAL NETWORK EXPERIENCE

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Background. Medication-related osteonecrosis of jaw (MRONJ) is a severe adverse drug effect, consisting of progressive bone destruction in the maxillofacial region, mostly caused by antiresorptive agents - including bisphosphonates and denosumab– and/or by antiangiogenic drugs[1]. Antiresorptive agents, also known as Bone Modifying Agents (BMAs) have demonstrated efficacy in limiting the osteolysis that occurs in many disorders characterized by increased bone resorption, including bone metastases and bone metabolic disorders. Incidence and/or prevalence of MRONJ in these categories of patients remain uncertain, with lack of solid epidemiologic data in large populations. As an almost unique experience, the aim of this work is to retrospectively describe number of registered cases and main features of MRONJ cases observed at main hospital oral care centres, in a time span of 15 years (2007-2021), in patients with non-malignant diseases, and observed in Piedmont and Valle d'Aosta territory (4.4 million inhabitants).

Patients and methods. Data were retrospectively collected from Oral Medicine, Oral Surgery and Oral Maxillofacial Surgery Units, from January 1st 2007, to 31st December 2021. The main parameters collected were: sex; age of patients at MRONJ diagnosis time; main disease for which BMAs were prescribed; received treatment: either bisphosphonates alone, or denosumab (60 mg q6 months), or bisphosphonate(s)/denosumab sequence; localization of MRONJ (mandibular and/or maxillary involvement).

Results. Over the 2007-2021 timespan, data from 184 patients were acquired; 173 (97.3%) were females; mean age was 75 years (range 37-94; standard deviation 9.81). Underlying disease was reported as osteoporosis in 161 (88%) patients, rheumatoid arthritis in 9 (5%), osteoporosis and rheumatoid arthritis in 8 (4%), or other bone disorders in 6 (3%), including lupus, Paget's disease, giant cell arthritis, etc.

Out of 184, 149 patients (81%) were treated with only one drug and 35 patients (19%) were treated with two BMAs in sequence.

In patients receiving one drug, the bisphosphonates most administered were alendronate (94), ibandronate (22) and risedronate (10). Ten patients were related to denosumab alone; the remaining 13 cases received clodronate, or neridronate, or pamidronate, or zoledronic acid alone.

In patients receiving sequence of drugs, the most used association were: alendronate followed by denosumab (10 cases), alendronate and ibandronate (5), and denosumab with ibandronate (5); the remaining cases were related to different combination of bisphosphonates with another bisphosphonate (12) or with denosumab (3).

Sites of MRONJ were in mandible (68.5%), maxilla (24.5%), or maxillary and mandible (7%).

Throughout the 15 years period of investigation, an increasing trend emerged, with a median of 11.5 (range 0-14) yearly MRONJ cases in the 2007-2014 period, increased to 17 (range 7-21) yearly MRONJ reported events in the 2015-2021 period.

Conclusions. MRONJ cases observed our oral care centres increased in frequency over the last 15 years among patients affected by bone metabolic disorders. Further studies are warranted to investigate the incidence and prevalence of MRONJ in patients undergoing low-dose bisphosphonates and low-dose denosumab.

[*]On behalf of oral care centers of: Turin, Novara, Alessandria, Asti, Cuneo, Orbassano, Aosta, Casale Monferrato, Vercelli

References

1. Bedogni et al. Italian position paper (SIPMO-SICMF) on medication-related osteonecrosis of the jaw (MRONJ). Oral Dis. 2024 Feb 5. doi: 10.1111/odi.14887. Online ahead of print.

MRONJ IN PATIENTS UNDER LOW-DOSE BONE MODIFYING AGENTS FOR CANCER TREATMENT-INDUCED BONE LOSS: A CASE SERIES

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Background. MRONJ is an adverse drug reaction mainly reported in two main categories of patients assuming Bone Modifying Agents (BMAs): cancer patients with bone metastases (BM) or multiple myeloma, commonly receiving high doses of BMAs (HD-BMAs), and patients suffering from osteoporosis receiving low doses of BMAs (LD-BMAs).
MRONJ risk categories have gradually changed due to the introduction of new medications to the market and the approval of supplementary indications for drugs already in use. Consequently, new categories of patients at risk of MRONJ were detected, including cancer patients without BM receiving LD-BMAs to reduce the risk of non-metastatic bone fractures due to Cancer Treatment-Induced Bone Loss (CTIBL).
CTIBL is the most common adverse event of patients affected by breast cancer (BC) or prostate cancer receiving adjuvant endocrine therapy. LD-BMA therapy is prescribed to them for CTIBL prevention, exposing them to MRONJ risk.
The study aims to describe the features of 7 BC patients under LD-BMAs for CTIBL with MRONJ, comparing them to 10 patients under LD-BMAs for osteoporosis with MRONJ.
Patients and methods. Patients were enrolled between May 2021 and December 2023 at the Oral Medicine Unit "V. Margiotta" of the University Hospital "Paolo Giaccone" in Palermo (Italy). Patients underwent clinical-radiological examinations. MRONJ was diagnosed and staged according to the Italian SIPMO-SICMF recommendations, based on clinical-radiological signs.
Results. The mean age of BC patients assuming LD-BMAs for CTIBL and patients assuming LD-BMAs with osteoporosis was 74.6 ± 5.2 years and 76.9 ± 6.8 years, respectively.
Regarding the BMAs, in CTIBL group, 2/7 patients received denosumab and 5/7 bisphosphonates; in osteoporosis group, 1/10 patients received denosumab and 9/10 bisphosphonates.
The mean duration of BMA therapy at the time of MRONJ development in CTIBL and in osteoporosis groups was 62.8 ± 70.6 months and 100.7 ± 78 months, respectively.
Regarding MRONJ stage, in CTIBL group, 3 patients were diagnosed in stage I, 1 in stage II, and 3 in stage III; while in osteoporosis group, 2 patients were diagnosed in stage I, 5 in stage II, and 3 in stage III.
The mandible was the most frequently affected site (4/7, 57.1% in CTIBL group *versus* 6/10, 60% in osteoporosis group).
Bone exposure was observed in four cases in CTIBL group (57.1%) and in eight cases in osteoporosis group (80%).
Conclusions. Patients assuming LD-BMAs for CTIBL prevention are an emerging category still poorly considered and often underestimated. The present preliminary study indicates that in this sample these patients develop MRONJ at a younger age and after a shorter BMA exposure duration compared to osteoporotic patients. This may be due to the systemic risk factors related to cancer disease, as well as the absence of specific prevention protocols tailored for this patient category. Additionally, in both groups, the prevalence of advanced MRONJ stages at the time of diagnosis indicates a poor early diagnosis. So, this study highlights the importance of MRONJ prevention for all types of risk categories, including patients under LD-BMA for CTIBL, as a borderline group, since at any time they can develop BM and therefore switch from LD-BMAs to HD-BMAs, increasing the MRONJ risk development.

References

1. Mauceri R, Coppini M, Attanasio M, Bedogni A, Bettini G, Fusco V, et al. MRONJ in breast cancer patients under bone modifying agents for cancer treatment-induced bone loss (CTIBL): a multi-hospital-based case series. BMC Oral Health. 2023 Feb 4;23(1):71.
2. Campisi G, Bedogni A, Fusco V. Raccomandazioni clinico-terapeutiche sull'osteonecrosi delle ossa mascellari (ONJ) farmaco-relata e sua prevenzione. Palermo: New Digital Press; 2020.
3. Bedogni A, Mauceri R, Fusco V, Bertoldo F, Bettini G, Di Fede O, Lo Casto A, Marchetti C, Panzarella V, Saia G, Vescovi P, Campisi G. Italian position paper (SIPMO-SICMF) on medication-related osteonecrosis of the jaw (MRONJ). Oral Dis. 2024 Feb 5. doi: 10.1111/odi.14887. Epub ahead of print. PMID: 38317291.

MRONJ IN PATIENTS WITH OSTEOPOROSIS AND NON-MALIGNANT DISEASES RECEIVING LOW DOSE ANTIRESORPTIVE AGENTS

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Background. Patients at risk of Medication-Related Osteonecrosis of the Jaw (MRONJ) include patients with bone metastases of cancer and myeloma patients, all receiving antiresorptive treatments (bisphosphonates or denosumab), known as Bone Modifying Agents (BMAs) with/without biological agents, but also patients with osteoporosis and other non-malignant diseases[1]. Since 2006, a MRONJ Multidisciplinary Team has been established in Alessandria Hospital, including: maxillofacial surgeons /dentists, oncologists, hematologists, nurses, radiologists, nuclear medicine and other medicine specialists, data managers[1]. We collected MRONJ cases among cancer patients and myeloma patients treated at our hospital with High-Dose BMAs (HD BMAs)[1], but also other patients receiving care at our centre if: a) MRONJ was suspected after treatment for cancer and myeloma in neighboring hospitals, or b) MRONJ was suspected among osteoporosis patients in the provincial territory by private practice dentists or physicians, after Low-Dose BMAs (LD BMAs).

Patients and methods. We updated our data, published in 2021[3], about more than 900 patients observed by members of the MRONJ Team, analyzing characteristics of cases confirmed as MRONJ according to Italian (SIPMO-SICMF) definition and recommendations[2], particularly about patients treated with LD-BMAs.

Results. We followed 130 MRONJ cases of confirmed MRONJ, found among patients receiving treatment with bisphosphonates and/or denosumab and/or antiangiogenics drugs, after both clinical and imaging evaluation. Second-level imaging was mostly based on Computed Tomography (CT scan).

Out of 130, 28 (21.5%) patients had been treated with LD-BMAs due to osteoporosis and other non-malignant disorders. Disease: 24 osteoporosis (alone or with other disease), 4 others (arthritis, Rheumatoid Arthritis, lupus). Status in January 2024: 24 alive, 4 dead.

Received treatment: alendronate alone in 9, denosumab (60 mg every 6 months) alone in 4, ibandronate in 5, pamidronate in 1, alendronate/denosumab sequence in 4, ibandronate/alendronate sequence in 2, other sequences of drugs in 3.

MRONJ diagnosis was registered: in years 2006-2010 (3 cases in 5 years), 2011-2015 (8 cases in 5 years), 2016-2020 (10 cases in 5 years), 2021-2023 (7 cases in 3 years).

Conclusions. In recent years we observed a slight increase of MRONJ cases observed in patients with osteoporosis and other non-malignant diseases (*i.e.*, rheumatic, autoimmune, etc.), mostly receiving "low dose" bisphosphonates and/or "low dose" denosumab.

Even if the individual risk is very different along their drug history (5-20% for metastatic cancer patients and myeloma patients, with higher values in long survivors, *versus* less than 1% in patients receiving "low dose" drugs), the large number of osteoporosis patients treated for several years justifies the observation of MRONJ cases among patients with osteoporosis and other non-malignant diseases.

References

1. Bedogni et al. Italian position paper (SIPMO-SICMF) on medication-related osteonecrosis of the jaw (MRONJ). Oral Dis. 2024 Feb 5. doi: 10.1111/odi.14887. Online ahead of print.
2. Campisi et al. Raccomandazioni clinico-terapeutiche sull'osteonecrosi delle ossa mascellari (ONJ)farmaco-relata e sua prevenzione at: https://www.sipmo.it/wp-content/uploads/2020/08/SICMF-SIPMO-2.0_web-con-cover-2020.pdf.
3. Fasciolo et al Prevention and screening of Osteonecrosis of Jaw (ONJ): the Alessandria experience of a multidisciplinary team on a 900-patient population. Qeios 2021 at: https://www.qeios.com/read/0QK8E2.