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COMMENT ON "MEDICATION-RELATED OSTEONECROSIS OF THE JAW (MRONJ)" BY ELIE M. FERNEINI IN THE SECTION "SIMPLY PUT: JOMS INFORMATION FOR PATIENTS"

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Dear Editor:—We read with great interest the contribute to the section "Simply Put: JOMS Information for Patients" named "Medication-Related Osteonecrosis of the Jaw (MRONJ)" by Elie M. Ferneini.[1]

We agree with the definition of MRONJ reported by the author that excludes any attempt to identify a specific clinical picture, although it was erroneously cited.[2] In fact, the reported description refers to the definition of osteonecrosis of the jaw originally introduced by the Italian Societies of Maxillo-facial Surgery (SICMF) and Oral Pathology and Medicine (SIPMO)[3] and later amended to include medications other than bisphosphonates: "Medication related osteonecrosis of the jaw (MRONJ) is an adverse drug reaction described as the progressive destruction and death of bone that affects the mandible and maxilla of patients exposed to the treatment with medications known to increase the risk of disease, in the absence of a previous radiation treatment."[4]

We agree with the need of a full cooperation between drug prescribers (eg, physicians) and oral and maxillofacial specialists to assess the individual need/timing of oral treatments and the likelihood of a temporary drug discontinuation.

However, we'd like to raise some concern about the following issues of the Ferneini's contribution, as they could confuse the reader:

- patients receiving antiresorptive agents at increased MRONJ risk and the type of medications reported;
- disease clinical presentation;
- the role of tooth extraction;
- the role of surgery.

In the light of current knowledge and with an open scientific debate still ongoing we would like to underline that:

- several groups of patients are at increased risk of MRONJ, with variable frequencies (ranging from < 1 to > 10%) due to different medications and not just bisphosphonates (denosumab above all); the likelihood of MRONJ occurrence typically

Table 1. GROUPS OF PATIENTS AT RISK OF MEDICATION-RELATED OSTEONECROSIS OF THE JAW (MRONJ)

Disease/Patients	Main Drug Treatments	Route of Administration
Primary osteoporosis Secondary osteoporosis Paget's disease, Rheumatoid arthritis	oral bisphosphonates (alendronate, risedronate, ibandronate) parenteral bisphosphonates (ie, yearly 5 mg zoledronic acid infusions; 6 mg ibandronate infusions) denosumab 60 mg every 6 months	os iv sc
Cancer patients (hormone-sensitive non-metastatic breast cancer and hormone-sensitive prostate cancer) at risk of treatment-induced bone loss. Ascertained Cancer Treatment Induced Bone Loss (CTIBL)	oral bisphosphonates (alendronate, risedronate, ibandronate) intravenous zoledronic acid (4 mg every 6 months; yearly 5 mg) denosumab 60 mg every 6 months	os iv sc
Cancer patients with bone metastases Multiple myeloma	monthly infusions of bisphosphonates (zoledronic acid, pamidronate, ibandronate) every 3 months infusions of zoledronic acid denosumab 120 mg every 4 weeks	iv iv sc
Giant cell tumor of bone	denosumab 120 mg every 4 weeks	sc
Cancer and noncancer patients receiving drugs associated with MRONJ other than antiresorptive drugs	sunitinib, bevacizumab, sorafenib, aflibercept, nivolumab, rituximab, regorafenib, everolimus, lenvatinib, imatinib, infliximab, etc.	various

Abbreviations: iv, intravenous; os, oral; sc, subcutaneous.

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increases with the time and correlates with drug exposure (treatment duration and number of administrations) (Table 1);

- bone exposure, the backbone of the most known definition of Osteonecrosis of the Jaw,[2] is only one of the possible signs of disease: many cases of MRONJ present with clinical signs and symptoms other than bone exposure, especially in the early phases, that can be promptly combined with imaging information of the underling bone (computed tomography) to support the final diagnosis. Bone exposure at the postextraction socket might be often triggered by a pre-existing bone necrotic process;
- the increased risk of developing MRONJ after tooth extraction might be related to an underlying pre−existing dental/periodontal infection rather than to the surgery per se.[5] Delaying the extraction of a compromised and infected tooth would increase the likelihood of MRONJ occurrence in many cases;
- surgical treatment of MRONJ is approved in several leading centers worldwide. Surgery can be curative long term. Nonsurgical treatment would be particularly appropriate in frail patients when reduction of symptoms (pain) and control of infection are pursued.[5]

We are confident that the inclusion of these information will improve this valuable contribution for patients and caregivers.

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