Review of: "Italian Position Paper (SIPMO-SICMF) on Medication-Related Osteonecrosis of the Jaw (MRONJ)"

Sotirios Tetradis[1]

1 University of California, Los Angeles

Potential competing interests: No potential competing interests to declare.

Dear Editor,

Thank you for the opportunity to review the Italian Position Paper on MRONJ. Overall, the manuscript is informative, thorough, well-written and utilizes evidence-based information to draw conclusions and make recommendations. If evidence is weak or lacking, the paper points this out when providing clinical best practice suggestions. Overall, an excellent work.

Below are themes in the position paper that I feel need to be clarified or modified.

- Definition Section

The second condition in the proposed definition states that a patient maybe considered to have MRONJ if there is presence of “Clinical and radiological findings of progressive bone destruction”. In the differential diagnosis, the presence of primary oral malignancy, metastatic disease or osteoradionecrosis are listed.

Numerous diseases can affect the orofacial complex and present with “progressive bone destruction”, including common periodontal and periapical disease and can occur in patients on antiresorptives. The MRONJ definition and differential diagnosis, as currently described in the Definition Section, could create confusion and lead to false positive (overdiagnosis) of the MRONJ. I recommend the Section be amended with a paragraph that clarifies this issue and states that “Clinicians must carefully consider and exclude all diseases with clinical and radiological findings of progressive bone destruction, including dental diseases such as periodontitis, periapical disease or peri-implantitis, or other diseases such as benign or malignant neoplasia, fibro-osseous conditions etc., from MRONJ”.

- Inclusion of anti-angiogenics (AAs) as medications associated with ONJ

In the position paper, four categories of patients associated with increased risk for MRONJ are recognized.

a. Cancer patients with Bone Metastases or Multiple Myeloma receiving monthly high doses (HD) of bone-modifying agents (BMAs) in combination with other drugs

b. Patients suffering from osteoporosis (OP) and other non-malignant diseases receiving low doses (LD) of BMAs

c. Cancer patients without bone metastases receiving LD-BMAs to reduce the risk of non-metastatic bone fractures,

and/or to improve prognosis

d. Patients with Giant Cell Tumour of Bone treated with a monthly injection of DMB (HD-DMB), who display an increased risk of MRONJ occurrence.

Patients on antiangiogenic without the use of antiresorptives are not listed in these four categories.

Furthermore, it is stated in the position paper that “risk estimates of MRONJ due to AAs could not be drawn from isolated reports and case series so far”. Similarly, the 2022 AAOMS position paper states “identifying a single medication as being the etiologic agent for MRONJ seems unlikely in case reports or mini-case series”.

Despite the above, the first criterion in the definition of MRONJ states that patients may be considered to have MRONJ if they are on “current or previous treatment with bone-modifying agents (BMAs) and/or antiangiogenic agents (AAs)”, a thesis that is repeated in multiple areas in the document. I find the position paper to be confusing on this point because of the diverse and sometimes contradictory statements regarding the association of AAs with ONJ. The position paper needs to clarify whether AAs should be considered as medications associated with MRONJ or not.

My personal opinion is that the evidence linking AA use alone with ONJ is weak, and as such at the current time AAs should not be included in the list of medications associated with MRONJ. Furthermore, even if we assume that AAs could be associated with ONJ, whether the pathophysiology of antiresorptive associated ONJ vs. AA associated ONJ is the same remains unknown. Given the different biological mechanisms of these classes of drugs, it seems likely these are two phenotypically similar conditions with distinctive etiology and pathogenesis that might require different approaches to treatment and prevention.

- Utilization of “bone marrow sclerosis” as a focal radiographic finding in MRONJ diagnosis and staging.

The use of bone marrow sclerosis as a necessary and sufficient radiographic finding of MRONJ is problematic. Bone marrow sclerosis alone, without the presence of other clinical or radiographic signs, could overestimate and in some cases underestimate the presence of MRONJ and the extent of the osteonecrotic area.

Trabecular sclerosis is a common finding in the jaws, particularly in the mandible, as a result of local inflammation due to dental infection, such as periapical or periodontal disease. These sclerotic changes can be quite extensive and can be present in patients who are not receiving antiresorptives, or in patients on antiresorptives without MRONJ. This sclerotic bone is vital, can remodel and can acquire normal morphology once the dental insult is removed. Even in patients with MRONJ, the bone with increased trabecular density likely remains vital, although remodeling of the sclerotic bone would be compromised because of the effects of the antiresorptive treatment.

In addition, trabecular sclerosis, although common, is not always present in patients with MRONJ. Some publications state that trabecular sclerosis is present in CT scans of all patients with MRONJ. However, other publications report that some patients with MRONJ do not show trabecular sclerosis.

Utilizing trabecular sclerosis as the sole radiographic finding to diagnose and stage MRONJ could be confusing and I am

concerned it will lead to inaccurate and poorly reproducible staging of MRONJ. For example, Figure 2 of the position paper shows a patient with Stage 1 MRONJ. However, close inspection of the coronal sections demonstrates increased trabecular density in the MRONJ site that engages the inferior alveolar canal and extends to the inferior border of the mandible, compared to the healthy right side. Based on the proposed staging in this position paper, this patient could/should be categorized as having Stage 2 disease.

My personal opinion is that the primary, essential radiologic signs of MRONJ include lytic erosive changes, non-healing extraction sockets, sequestration, and periosteal bone formation; these features closely associate with the osteonecrotic area. Increased trabecular density, thickening of the lamina dura, and cortical hyperostosis without periosteal reaction or expansion are secondary radiologic findings reflecting bone deposition not opposed by osteoclastic function. These secondary findings reveal the extent of the inflammatory signals that activate osteoblasts, but do not in and of themselves necessarily indicate the presence of bone necrosis.

I thus would recommend the expert panel expand the radiographic findings required to diagnose and stage MRONJ and rethink the significance of “bone marrow sclerosis” as a necessary and sufficient parameter for the diagnosis and staging of the disease.

Minor comments

- Use of the term “dental x-rays”

Consider replacing the term “dental x-rays” with “intraoral radiographs” throughout the document. “Intraoral radiographs” is the correct term to describe periapical and bitewing radiographs used in everyday dental practice.

- Consider replacing the statement “Despite the histology of bone can easily disclose necrotic bone from viable bone also in MRONJ patients …” with “Although histology can distinguish between necrotic vs. viable bone, in MRONJ patients …”
- It is stated that “The use of bone biopsy in the diagnostic work-up of MRONJ is only indicated to disclose the suspect of malignancy”. Even when malignancy is suspected, the jaw lesion most likely represents a metastasis of the systemic disease. A PET-CT should be performed prior to biopsy to assess dissemination of wide-spread metastasis. If metastatic disease is established biopsy could be avoided.
- Consider replacing the statement “To date, prevention of MRONJ remains the most effective strategy by which to protect the oral health of patients before the initiation, during and after treatment with medications associated with an increased risk of MRONJ.” with “To date, oral health preventive measures remain the most effective strategy to prevent MRONJ prior to, during and after the initiation of treatment with medications associated with an increased risk of MRONJ.”
- Consider replacing the statement “due to its known long-standing inhibition of jawbone remodeling” with “due to the known long-standing inhibition of jawbone remodeling by BPs”.
- Consider replacing the statement “poor adherence to antiresorptive treatments is likely to be expected, being these medications perceived as potentially dangerous by patients.” with “poor adherence to antiresorptive treatments is likely,

since these medications are perceived as potentially dangerous by patients.”

Thank you again for the opportunity to review this well thought-out and informative position paper on a very significant clinical disease.

Best regards,