Proceedings of the closed round table and *Italian Consensus* on the Medication-Related OsteoNecrosis of Jaws (MRONJ) at the Symposium of Italian Society of Oral Pathology and Medicine (SIPMO) Ancona, 20 October 2018 – Part III

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E. Practices at risk of inappropriateness in drug holiday (temporary suspension vs therapeutic suspension for patients at risk of MRONJ). Yes vs No

The Drug Holiday is a controversial issue (due to inconsistent literature data), involving both drug prescribers (e.g. oncologists, hematologists, bone health specialists, general practitioners) and oral and dental specialists. Consequently, some assumptions are to be underlined.

"Drug holiday" can have different meanings in medical literature when referred to MRONJ. We have to distinguish:

a) Temporary and preventative suspension of drug therapy (e.g. bisphosphonates, denosumab, and sometimes antiangiogenic drugs) in a patient at risk of MRONJ, in case of dentistry procedures (e.g. tooth extraction or jawbone surgery) potentially inducing or highlighting jawbone necrosis (with/without bone exposure); frequently the feared MRONJ risk is due to both prolonged treatment and bone trauma;

b) Suspension of drug therapy (e.g. bisphosphonates, denosumab) after established diagnosis of MRONJ, hypothetically finalized to stop or to slow osteonecrosis process;

c) Suspension of drug therapy (bisphosphonates, denosumab) potentially inducing MRONJ after a supposed unfavorable cost-benefit balance, due to lowered efficacy or increased real (or feared) side effects; for example, due to fear of MRONJ or atypical femur fracture after several years of bisphosphonate or denosumab treatment.

As the second and the third meaning have scarce literature data at this moment, this document will only afford the first meaning of "drug holiday".

Two different populations are usually recognized as at risk of MRONJ due to antiresorptive treatment (e.g. bisphosphonates, denosumab), even with very different MRONJ incidence:

i) Cancer and myeloma patients with bone disease receiving antiresorptive drugs at higher doses and more frequently (e.g. monthly 4mg i.v. zoledronic acid, or monthly 120mg s.c. denosumab administration);

ii) Osteometabolic patients and people affected by other nonmalignant diseases (osteoporosis, Paget disease, etc.) receiving antiresorptive drugs at lower doses and less frequently (e.g. oral bisphosphonates; yearly 5mg i.v. zoledronic acid; bi-yearly 60mg s.c. denosumab).

Consequently, the distinctive MRONJ risk of these two patient populations reflects on different evaluation of possible "Drug Holiday".

However, it is to be noted that some special patient subsets escape this dichotomy:

- Patients suffering from RA (Rheumatoid Arthritis), showing higher MRONJ risk than osteoporosis patients;

- Cancer patients (i.e. breast and prostate cancer patients) receiving preventative low-dose antiresorptive drugs due to risk of CTIBL (Cancer Treatment Induced Bone Loss), with MRONJ risk next to that of osteoporotic patients;

- Cancer patients receiving both antiangiogenic and high dose antiresorptive drugs, at even higher MRONJ risk than those receiving only antiresorptive therapy.

Furthermore, the evaluation for a possible drug holiday has to consider that the ONJ risk sensibly depends on drug exposure time (years of administration) and the observation time (time since the initial administration) in both two main patient populations: active cancer and myeloma patients, and osteoporotic patients.

Finally, a careful imaging study of the patient (i.e. by Computed Tomography exams) is recommended before balancing pros and cons of drug holiday in case of tooth extraction (or other bone trauma) in a symptomatic patient at risk of ONJ.

Practices at risk of inappropriateness

#1 performing dental extraction or oral surgery in patients with active cancer and myeloma bone disease and in therapy with i.v. high-dose bisphosphonates without concerting any temporary suspension (drug holiday) with the prescriber (oncologist / haematologist)

#2 suspending indiscriminately therapy with antiresorptive drugs (i.e. bisphosphonates, denosumab) prescribed for osteoporosis (or its prevention), at least in the first three years of assumption, in case of necessity of extraction or programmed oral surgery

#3 performing dental extraction or oral surgery in patient with active cancer and myeloma bone disease and in therapy with denosumab without concerting any temporary suspension (drug holiday) with the prescriber (oncologist / haematologist)

Good practices

#1 plan, in cancer patients, combined assessment by prescriber (i.e. high risk versus low risk of fracture and other SREs, Skeletal-Related Events) and by dentist (i.e. high risk versus low risk of post-extraction complications) to determine whether or not the need for precautionary suspension of i.v. high-dose bisphosphonate, before and after the dental management. This combined assessment is mandatory in the absence of univocal data on the efficacy and need to suspend zoledronic acid or other bisphosphonates to reduce the risk of "post-extraction" ONJ, and in consideration of conflicting data on the anti-angiogenic effect of zoledronic acid [1–4].

#2 plan, in osteometabolic patients, combined assessment by prescriber (i.e. high risk versus low risk of fracture)* and by dentist (i.e. high risk versus low risk of post-extraction complications) to determine whether or not the need for precautionary suspension of the drug, before and after the dental procedure. In particular, to evaluate mutually the risk-benefit ratio (probability of fracture** versus probability of ONJ) if the therapy continues for over three years.

#3 plan, in cancer patients, combined assessment by prescriber (i.e., high risk versus low risk of fracture and other SREs, Skeletal-Related Events) and by dentist (i.e. high risk versus low risk of post-extraction complications) to determine whether or not the need for precautionary suspension of denosumab, before and after the dental management, with careful monitoring of a possible "rebound" effect after discontinuation of denosumab. This is mandatory in the absence of univocal data on the efficacy and on the need to suspend denosumab to reduce the risk of ONJ after surgical procedures. We remind what reported in one recent myeloma trial of denosumab versus zoledronic acid: "administration of the study

drug (subcutaneous and intravenous) was withheld 30 days before any elective invasive oral or dental procedures and complete until mucosal healing occurred" [8-10].

F. Practices at risk of inappropriateness in MRONJ therapy and good practices

The MRONJ Italian Consensus embraced the principles and good practices promoted by the SIPMO/SICMF ONJ Board with respect to therapeutic strategies [11,12].

In particular, the following hot topics were discussed and capitalized: #1 perioperative antibiotic regimen; #2 bone biopsy in patients suffering from clinical-radiological evidence of MRONJ; #3 role of preoperative imaging; #4 anticipated surgery versus planned exfoliation (self-sequestration); #5 the shaving and smoothing of bone surfaces during surgical therapy; #6 surgery-related quality of life issues for MRONJ patients; #7 impact of the type of medication on the treatment decision-making of patients with BP-related and non-BP related (anti-RankL and/or targeted therapies) MRONJ; #8 surgery for asymptomatic MRONJ; and #9 role of bone turnover markers for surgery.

Practices at risk of inappropriateness

#1 forgetting the adoption of adequate perioperative antibiotic regimen in case of surgical treatment of MRONJ.

#2 performing a diagnostic bone biopsy, unless bone metastases are suspected.

#3 applying of first-level imaging (e.g. dental x-ray and panoramic radiograph) only to plan surgical treatment.

* The fracture risk can be determined objectively and correctly by applying the DeFRA79 algorithm validated by AIFA (www.defra-osteoporosi.it), Italian version of the FRAX algorithm.

** The suspension of denosumab determines within the 3-6 following months a rebound of the fracture risk especially in patients at high risk of fracture (those provided for denosumab by the AIFA therapeutic plan) [5–7].

#4 awaiting the exfoliation (i.e. self-sequestration) of necrotic exposed bone via the use of non-surgical therapies, since this process is unpredictable over time.

#5 neglecting shaving and smoothing of the bone surfaces as a mainstay of any surgical procedure

#6 banishing the surgical option for MRONJ cancer patients based on general statements of residual life expectancy.

#7 merging BP-related and non-BP-related (e.g. anti-RankL and/or targeted therapies) MRONJ patients as a whole when considering temporary interruption of medications for surgical treatment.

#8 adopting surgical treatment of MRONJ in symptomatic cases only.

#9 relaying on systemic bone turnover markers to predict the success of surgical therapies in MRONJ patients.

Good practices

#1 prescribe a broad-spectrum antibiotic regimen as an integral part of surgical treatment: high-dose amoxicillin/clavulanic acid (1000mg TID), plus high-dose Metronidazole (500 mg TID), from the day before surgery and up to the 10th post-operative day. Alternatives should be used in case of reported allergy to penicillin.

#2 perform a diagnostic bone biopsy in case of clinical and radiological suspicion of bone metastases to the jaw.

#3 use of second-level imaging, mainly computed tomography (CT), to appropriately plan the extent of jawbone disease before surgery.

#4 anticipate surgical treatment whenever indicated, to reduce the surgical burden for MRONJ patients and increase the likelihood of long-term healing.

#5 always perform the shaving and smoothing of bone surfaces as a mainstay of any surgical procedure to prevent further bone exposure.

#6 plan the surgical treatment of MRONJ on an individual basis, weighing the impact and the potential benefit of surgery on the general health status of patients.

#7 discuss and plan the temporary interruption of any given medication in agreement with the prescriber and based on its pharmacological properties, before initiating every MRONJ surgical treatment.

#8 adopt the early surgical treatment also in MRONJ asymptomatic patients.

#9 do not rely on systemic bone turnover markers to establish individual treatment algorithm for MRONJ, but carefully examine all potential factors that are likely to influence the long-term success of therapies, including the underlying disease (cancer or non-cancer) and the type of medication used.

Keywords: MRONJ, ONJ (Osteonecrosis of the Jaws), BRONJ (BisphosPhonate-Related Osteonecrosis of the Jaw), risk of inappropriateness, MRONJ Italian Consensus, SIPMO, SIdCO

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