




Letter to the Editor

Consensus of AIMOM (Association Internationale de Médecine Orale et Maxillo-faciale) on the management of drug-related osteochemonecrosis of the jaws in 2024

Anaïs Protin^{1,2} , Antony Alcacer³, Thomas Wojcik^{1,4}, Nathalie Pham Dang^{3,5}, Laurent Devoize^{3,5} , Joel Ferri^{1,2,4*} 

¹ CHU Lille, Service de Stomatologie, de chirurgie orale et maxillo-faciale, 59000, Lille, France

² Département universitaire de Stomatologie, de Chirurgie orale et maxillo-faciale Université de Lille UFR3S, 59000, Lille, France

³ University Hospital of Clermont-Ferrand, CHU Clermont-Ferrand, Department of Oral and Maxillofacial surgery, 63000, Clermont-Ferrand, France

⁴ CHU Lille, Inserm U1008 - Controlled Drug Delivery Systems and Biomaterials, 59000, Lille, France

⁵ UMR Inserm/UdA, U1107, Neuro-Dol, Trigeminal Pain and Migraine, Université d'Auvergne, 63003, Clermont-Ferrand, France

(Received: 27 May 2024, accepted: 31 May 2024)

Drug-related osteonecrosis of the jaws, more commonly called OsteoChemoNecrosis (OCN), is defined by the American Association of Oral and Maxillofacial Surgeons (AAOMS, 2014) as an oral complication in patients who meet the following criteria:

- Ongoing treatment (or history of treatment) with antiresorptive agents (bisphosphonates, anti-RANKL) or antiangiogenic agents;

- Bone exposure or bone that can be probed by an intraoral or extraoral fistula in the maxillofacial region and that persists for more than 8 weeks;

- Absence of radiotherapy of the jaws or metastatic lesions.

The staging of OCN incorporates patient-reported symptoms, clinical lesion assessment, and radiological imaging.

In the initial stage (stage 0), no clinical evidence of necrotic bone is apparent; patients exhibit non-specific clinical and/or radiological symptoms or signs [1]. In stages 1 (focal OCN) and 2 (diffuse OCN), patients can be asymptomatic (1a-2a) or symptomatic with pain/infection (1b-2b). At stage 3, OCN is complicated with the presence of extra-oral fistula, spontaneous fracture, etc.

The pathophysiology of OCN remains incompletely understood, leading to a lack of consensus in its management. The only aspects subject to expert opinion are:

- the risk of OCN must be assessed before and during any OCN-inducing treatment.

- the assessment of the risk of OCN as well as its treatment are based on a multidisciplinary approach involving dentists, general practitioners, rheumatologists, oncologists, oral and maxillofacial surgeons, nurses, and the patient [2,3].

The decision to stop an antiresorptive treatment must be decided after evaluating the benefits and risk of this decision.

Key points

Molecules at the origin of OCN are anti-RANKL (Denosumab) with 70.3% of cases reported in France between 2015 and 2020, amino-bisphosphonates (zoledronic acid (23%) and alendronate (8.7%)) when used in high dose for oncological treatment [4].

Location

Whatever the molecules involved, the mandible is the most frequently affected [4].

Management of denosumab-induced osteochemonecrosis

Stopping Denosumab alone is often sufficient to obtain spontaneous healing in a duration of 6 to 8 months.

This phenomenon can be attributed to the longer half-life of bisphosphonates (estimated at 10 yr for zoledronic acid)

* Correspondence: ferri.joel@gmail.com

compared to anti-RANKL (28 days for denosumab). Bone remodeling physiology typically returns to normal shortly after discontinuing denosumab, unlike bisphosphonates [5].

Osteometabolic control is recommended, it consists of the balance of biomarkers involved in bone renewal: PTH, CTX, osteocalcin, vitamin D, calcium, vitamin K, to optimize the chances of healing OCN [6]. The use of PTH (Teriparatide) as an osteogenesis inducer should be moderated or even avoided if the patient with active cancer [7].

Conservative treatment

OCN often occurs in a context of associated tumor pathology, explaining that the patient quality of life is the priority. Symptomatic relief is most often obtained with conservative, non-invasive treatment.

Prolonged conservative treatment (1 yr) with local antiseptics (Chlorhexidine rinsing 7 consecutive days each month) and antibiotic therapy (Amoxicillin/Clavulanic Acid (875/125 mg 3 times a day) and Metronidazole (500 mg 3 times a day) for 7 days if suppuration) allows lasting improvement of signs and symptoms [8].

To improve the condition of ischemic tissues, the use of Tocopherol (antioxidant) and Pentoxifylline (antifibrotic) can be useful for the conservative treatment in addition to antiseptics and antibiotics (Amoxicillin +/- Clavulanic Acid, Clindamycin, Metronidazole) during secondary infections [6,7,9]. Pentoxifylline has no longer been available in some countries since 2023, others continue to use it.

Two recent literature reviews published in 2019 and 2021 also show the effectiveness on pain and necrosis of the use of hyperbaric oxygen therapy [10,11]. This therapy before and after surgery seems effective, specifically in the clinical aspect of the lesions, but today this procedure cannot be validated.

Non-conservative treatment

Surgical treatment is proposed for stages 2 and 3 when conservative treatments failed or when healing of the mucous membranes is the goal.

However, there is no consensus on surgical procedures [12]. The most frequently proposed surgical treatments are sequestrectomy or resection of necrotic tissues with perfect closure of the mucosa.

Surgical interventions can be augmented by PRP/PRGF/PRP-L/PRF-L, frequently utilized adjunctive therapies aimed at enhancing soft tissue healing and bone regeneration. They would improve the outcome of soft tissue healing and bone regeneration [7,13,14].

The use of photodynamic therapy (photobiomodulation) appears to be effective as an adjuvant treatment to surgery t at stages 2 and 3 [15–18] and promoting sequestration [10,14].

Most studies included patients affected in the mandible with stage 2. They demonstrated a complete recovery for the majority of patients when photobiomodulation (Nd:YAG,

GaIAs) was combined with surgery [19,20]. Addition of PRF was also used to help surgical healing [21,22]. Laser surgery (Er:Yag) also seems to be an effective alternative [23,24]. For stage 1, photobiomodulation used alone would be effective as a conservative treatment [17].

Fluorescence-guided surgery is promising [13,16,17]. There is no need to apply exogenous fluorophore and the most used light device was the VELScope® system [17]. Sometimes preoperative doxycycline is used, which can be detected by a fluorescent light source [7]. This technique makes it possible to spare healthy tissue. Indeed, it could differentiate necrotic areas from the alive ones.

Conclusion

OCN is a complication of antiresorptive treatments (bisphosphonates, anti-RANKL) used mainly in the context of tumor pathology. An oral assessment and long-term monitoring of the patient by his oral health professional makes it possible to assess the risks of OCN. In this context, dental and periodontal care can be carried out in a general practice, with dental extractions preferably being carried out in a hospital with antibiotic prophylaxis.

In most cases, conservative management should be preferred.

Funding

The authors received no financial support for the research and publication of the article.

Conflicts of interest

The authors declared no potential conflicts of interest with respect to research and publication of the article.

Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

References

1. Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B, *et al.* American association of oral and maxillofacial surgeons position paper on medication-related osteonecrosis of the jaw-2014 update. *J Oral Maxillofac Surg* 2014;72:1938–1956.
2. Otto S, Pautke C, Van den Wyngaert T, Niepel D, Schiødt M. Medication-related osteonecrosis of the jaw: Prevention, diagnosis and management in patients with cancer and bone metastases. *Cancer Treat Rev* 2018;69:177–187.
3. Yao S, Ding X, Rong G, Zhou J, Zhang B. Association between malignant diseases and medication-related osteonecrosis of the jaw (MRONJ): a systematic review and meta-analysis. *J Craniofac Surg* 2023;34:669–673.
4. Legendre Q, Faillie J, Lapeyrie P, Tramini P, Maladiere E, Torres JH, *et al.* Epidemiology of osteochimionecrosis of the jaws in

- France, update of data since 2015. *J Stomatol Oral Maxillofac Surg* 2022;123:e448–e453.
5. Ohga N, Sato J, Asaka T, Morimoto M, Yamazaki Y, Kitagawa Y. Successful conservative treatment of jaw osteonecrosis caused by denosumab in patients with multiple bone metastasis. *J Oral Sci* 2018;60:159–162.
 6. Colapinto G, Volpi R, Forino G, Tricarico V, De Benedittis M, Cortelazzi R, *et al.* Patients' osteometabolic control improves the management of medication-related osteonecrosis of the jaw. *Oral Surg Oral Med Oral Pathol Oral Radiol* 2018;125:147–156.
 7. Goker F, Grecchi E, Grecchi F, Francetti L, Del Fabbro M. Treatment of medication-related osteonecrosis of the jaw (MRONJ). A systematic review. *Eur Rev Med Pharmacol Sci* 2021;25:2662–2673.
 8. Albanese M, Zotti F, Capocasale G, Bonetti S, Lonardi F, Nocini PF. Conservative non-surgical management in medication related osteonecrosis of the jaw: a retrospective study. *Clin Exp Dent Res* 2020;6:512–518.
 9. Cavalcante RC, Tomasetti G. Pentoxifylline and tocopherol protocol to treat medication-related osteonecrosis of the jaw: a systematic literature review. *J Craniomaxillofac Surg* 2020;48:1080–1086.
 10. Watanabe T, Asai K, Fukuhara S, Uozumi R, Bessho K. Effectiveness of surgery and hyperbaric oxygen for antiresorptive agent-related osteonecrosis of the jaw: a subgroup analysis by disease stage. Al-Moraisi E, rédacteur. *PLoS ONE* 2021;16:e0244859.
 11. De Souza Tolentino E, De Castro TF, Michellon FC, Passoni ACC, Ortega LJA, Iwaki LCV, *et al.* Adjuvant therapies in the management of medication-related osteonecrosis of the jaws: systematic review. *Head Neck* 2019;41:4209–4228.
 12. Kagami H, Inoue M, Kobayashi A, Taguchi A, Li X, Yoshizawa M. Issues with the surgical treatment of antiresorptive agent-related osteonecrosis of the jaws. *Oral Dis* 2018;24:52–56.
 13. Zigmantavičius J, Kilinskaitė G, Kubilius R. Surgical treatment methods of medication-related osteonecrosis of the jaw. A systematic review. *Stomatologija* 2022;24:91–99.
 14. Pardo-Zamora G, Martínez Y, Moreno JA, Ortiz-Ruiz AJ. Treatment of stage 2 medication-induced osteonecrosis of the jaw: a case series. *Int J Environ Res Public Health* 2021;18:1018.
 15. De Santis D, Gelpi F, Luciano U, Zarantonello M, Poscolere A, Modena N, *et al.* New trends in adjunctive treatment and diagnosis in medication-related osteonecrosis of the jaw: a 10-year review. *J Biol Regul Homeost Agents* 2020;34:37–48.
 16. Huang H, Zhao N, Li Q, Zhang QQJ, Guo C, Guo Y. The therapeutic effectiveness using fluorescence-guided surgery for MRONJ. *Biomed Res Int.* 2022;2022:1650790.
 17. Tomo S, da Cruz TM, Figueira JA, Cunha JLS, Miyahara GI, Simonato LE. Fluorescence-guided surgical management of medication-related osteonecrosis of the jaws. *Photodiagnosis Photodyn Ther.* 2020;32:102003.
 18. Tandon S, Lamba AK, Faraz F, Aggarwal K, Chowdhri K. A case report of bisphosphonate related osteonecrosis of the jaw treated by photodynamic therapy. *Photodiagnosis Photodyn Ther* 2019;26:313–315.
 19. Şahin O, Akan E, Tatar B, Ekmekcioğlu C, Ünal N, Odabaşı O. Combined approach to treatment of advanced stages of medication-related osteonecrosis of the jaw patients. *Braz J Otorhinolaryngol* 2022;88:613–620.
 20. Tartaroti NC, Marques MM, Naclério-Homem M da G, Migliorati CA, ZindelDeboni MC. Antimicrobial photodynamic and photobiomodulation adjuvant therapies for prevention and treatment of medication-related osteonecrosis of the jaws: case series and long-term follow-up. *Photodiagnosis Photodyn Ther* 2020;29: 101651.
 21. Nica DF, Riviş M, Roi CI, Todea CD, Duma VF, Sinescu C. Complementarity of photo-biomodulation, surgical treatment, and antibiotherapy for medication-related osteonecrosis of the jaws (MRONJ). *Medicina* 2021;57:145.
 22. Tenore G, Zimbalatti A, Rocchetti F, Graniero F, Gaglioti D, Mohsen A, *et al.* Management of medication-related osteonecrosis of the jaw (MRONJ) using leukocyte- and platelet-rich fibrin (L-PRF) and photobiomodulation: a retrospective study. *J Clin Med* 2020;9:3505.
 23. Merigo E, Cella L, Oppici A, Cristina Arbasi M, Clini F, Fontana M, *et al.* Combined approach to treat medication-related osteonecrosis of the jaws. *J Lasers Med Sci* 2018;9:92-100.
 24. Momesso GAC, Lemos CAA, Santiago-Júnior JF, Faverani LP, Pellizzer EP. Laser surgery in management of medication-related osteonecrosis of the jaws: a meta-analysis. *Oral Maxillofac Surg* 2020;24:133–144.