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Research Article

Bisphosphonates Related Osteonecrosis of the Jaw: Systematic Review of the Literature

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Abstract

Objectives: The aim of this review is to assess the route of administration of bisphosphonates (BPs) most likely to generate osteonecrosis of the jaw (ONJ) while determining the profile of patients receiving this type of treatment.

Methods: A literature search in PubMed, EMBASE and Cochrane of randomized controlled clinical trials, systematic reviews and meta-analyzes was carried out between 2007 and 2018 using the terms bisphosphonates (BPs), oral, intravenous and osteonecrosis of the jaws.

The number of publications by year, type of publication and level of proof of the articles were assessed. Likewise, the incidences of occurrence of ONJ according to each route of administration of BPs and the profile of patients receiving this treatment were identified.

Results: 3456 publications published since 2007, mainly in oncology and maxillofacial journals, were reviewed. 6 publications whose level of proof corresponds to our objective were selected.

Discussion: Studies have shown a wide variety in design and a strong incidence of ONJ depending on the route of administration of Bps. A higher prevalence has been observed following intravenous administration.

Keywords: Osteonecrosis of the Jaw; Bisphosphonates; Oral Route; Venous Route

Introduction

BPs-induced ONJ was first defined in 2007 by the American Association of Oral and Maxillofacial Surgeons (AAOMS) [1,2].

Three main characteristics make it possible to differentiate ONJ from delayed bone healing: patient recently or having previously received treatment with Bps, presence of necrotic bone exposure in the maxillofacial region that persists for more than eight weeks and absence of medical history of head and neck radiotherapy [2].

The first series of ONJ cases was published in 2003 by Marx and in 2004 by Ruggiero., *et al* [3,4]. Subsequently, several publications concerning ONM have emerged. The pathophysiology is not yet clear, common theories suggest a reduction in bone remodeling, an alteration of local vascularization and neoangiogenesis, an accumulation of microcracks and therefore infection of the bone via bone resorption independent of osteoclasts.

The symptomatology associated with ONJ induced by bisphosphonates is variable, it depends on the phase of development. In 2007, AAOMS established a classification of ONJ with 3 stages:

- Stage 1: Apparent bone necrosis in asymptomatic patients without associated infection.
- Stage 2: Apparent bone necrosis associated with infection with the presence of pain and erythema in the exposed area with or without purulent discharge.

- Stage 3: Apparent bone necrosis associated with one or more of the following signs: apparent bone necrosis extending beyond the alveolar bone (basilar edge and posterior edge of the mandibular ramus, maxillary sinus and zygoma) resulting in fracture, extra-oral fistula, oro-antral communication, or osteolysis extending to the lower mandibular border or sinus floor.

In 2009, AAOMS established a new classification adding a stage 0: no apparent clinical sign of bone necrosis but presence of non-specific clinical signs and symptoms [2].

BPs can be prescribed orally (VO) in the first place for benign pathologies such as osteoporosis with recourse to the venous route in case of patient intolerance. The intravenous (IV) route is more frequently used in malignant pathologies, for the treatment of breast, prostate, genitourinary, or gastrointestinal cancer, as well as in cases of multiple myeloma and bone metastases.

The occurrence of ONJ following the use of BPs is most often caused by a major triggering factor such as tooth extraction or other trauma to the oral cavity. Osteonecrosis is frequently localized in the mandibular premolo-molar region, the cortical bone is thicker and less vascularized in this area.

Due to the disparity in the incidence of this pathology, which varies between 0.01% and 6.7% worldwide, we carried out a systematic review of the literature with the objective of evaluating the route of administration of bisphosphonates that generate the most osteonecrosis of the jaw and to determine the profile of patients who receive bisphosphonate treatment [1].

Materials and Methods

A systematic search was performed on the PubMed, Embase and Cochrane databases. The main ideas of the research topic were: Osteonecrosis of the jaw, Bisphosphonates and route of administration (intravenous or oral route).

Using the various keywords and Boolean equations, a total of 3456 articles were found. After eliminating, using the search filters, results with a publication date prior to 2007 as well as experimental animal studies, clinical case reports and case series, 902 publications were retained corresponding to comparative clinical studies, clinical trials, meta-analyzes, randomized controlled trials and systematic reviews. Following a methodological critical reading, by double reader, and the exclusion of irrelevant articles, 6 articles were selected for the study.

Results

The retained articles were mainly from English-language journals (Table 1).

N°	Author	Title	Review	Country	Year
1	Petra Rugani, Gero Luschin, Norbert Jakse, Barbara Kirnbauer, Uwe Lang, Stephan Acham.	Prevalence of bisphosphonate-associated osteonecrosis of the jaw after intravenous zoledronate infusions in patients with early breast cancer.	Springer-Verlag Berlin Heidelberg.	Austria	2013
2	Peter Gimsing, Kristina Carlson, Ingemar Turesson, Petrer Fayers, Anders Waage, Annette Vangsted, Anne Mylin, Christian Gluud, Gunnar Juliusson, Henrik Hjorth-Hansen, Ingerid Nesthus, Inger Marie S Dahl, Jan Westin, Johan Lanng Nielsen, Lene Meldgaard knudsen, Lucia Ahlberg, Martin Hjorth, Niles Frost Andersen, Olle Linder, Fin Wisloff.	Effect of pamidronate 30 mg versus 90 mg on physical function in patients with newly diagnosed multiple myeloma (Nordic Myeloma Study Group) : a double-blind, randomised controlled trial.	The lancet Oncology.	Denmark, Norway, Sweden	2010
3	Thomas Mucke, Herbert Deppe, Jana Hein, Klaus-Dietrich Wolff, David A.Mitchell, Marco R.Kesting, Margitta Retz, Jurgen E.Gschwend, Mark Thalgott.	Prevention of Bisphosphonate-Related Ostonecrosis of the jaws in patients with prostate cancer treated with Zoledronic acid (a prospective study over 6 years).	Journal of Cranio-Maxillo-Facial Surgery.	Germany	2016
4	James S. Goodwin, Jie Zhou, Yong-Fang Kuo, Jacques Baillargeon.	Risk of jaw Osteonecrosis after intravenous bisphosphonates in cancer patients and patients without cancer.	Mayo Foundation for Medical Education and Research.	America	2017

5	D.H. Solomon, E.Mercer, S.B.Woo, J.Avorn, S.Schneeweiss, N.Treister.	Defining the epidemiology of bisphosphonate-associated osteonecrosis of the jaw: prior work and current challenges.	International Osteoporosis Foundation and National Osteoporosis Foundation	USA	2012
6	T. Shintani, Y. Hayashido, H.Mukasa, E. Akagi, M. Hoshino, Y. Ishida, T.Hamana, K. Okamoto, T. Kanda, K. Koizumi, Y. Yoshioka, R. Tani, S. Toratani, T. Okamoto.	Comparison of the prognosis of bisphosphonate-related osteonecrosis of the jaw caused by oral and intravenous bisphosphonate.	International Journal of Oral and Maxillo-facial Surgery.	Japan	2015

Table 1: Summary table of the articles selected.

Regarding demographic and clinical data for the 6 selected studies, the mean sample value was 89,829.5. The average age group of the study population was 51 years, ranging from 35 to 92 years, with a female predominance (Table 2).

Study number	Sample size	Age	Sex
1	100	43 - 60 years	Women
2	504	53 - 87 years	Women: 200
			Man: 304
3	253	46 - 92 years	Man
4	29 459	65 - 85 years	Women: 26 250
			Man: 3209
5	508 602	34 years	-
6	59	67 years	Women: 39
			Man: 20

Table 2: Age, sex and size of the samples studied.

Zoledronic acid by the intravenous route was the most widely used molecule in 3 of the studies selected with a dosage of 4 mg/month for 3 years with a reduction in the dose in cases of renal failure, followed by pamidronate in a multicenter clinical trial at double blind (study 2) (30 mg or 90 mg/month for 3 years).

Only two studies used both routes (oral and intravenous) for the treatment of benign pathologies such as osteoporosis and Paget's disease over an average duration of 61 months (Etidronate, Ibandronate, Résidronate, Minodronate) and malignant with an average of 25 months (Alendronate, Pamidronate and zoledronic acid) (studies 4 and 6) (Table 3).

Four selected studies (1, 2, 3, 5) where BPs were administered only intravenously revealed the occurrence of ONJ with an average of 16 cases.

Two studies (4.6) using both oral and IV routes reported an average of 53 cases with ONJ.

All studies using the IV route have revealed a fairly large number of cases with ONJ with preferential mandibular localization.

The occurrence of ONJ can only be confirmed by the correlation of clinical and radiological signs which differ according to the stage of ONJ (Table 4).

Discussion and Conclusion

ONJ was first described by AAOMS in 2003 by highlighting the presence of three main characteristics. A single article, published by Thomas Mücke., *et al*. adopted this classification in the diagnosis of ONJ, thus confirming the occurrence of 40 cases after administration of zoledronic acid by IV route [5]. The use of the AAOMS 2007 classification allowed D. H. Solomon., *et al*. to confirm the diagnosis of 8 cases of ONJ induced by BPs [6].

In the studies by Petra Rugani., *et al*., James S. Goodwin., *et al*. and T. Shintani, the authors used the latest AAOMS classification (2009) in order to minimize the margin of error in determining the incidence of ONJ. 5 cases were diagnosed in the first study [7], 48 cases under IV BPs in the second [8] and 59 cases in the last study (27 cases in the group treated with BP by VO and 32 cases in the group treated with by BP IV) [9]. In addition, only one study, by Peter Gimsing., *et al*. did not specify the classification used. The comparison of the cases was based on the dosage of BPs used intravenously (pamidronate 30 mg vs 90 mg) [10].

With regard to socio-demographic characteristics, the difference in age and sex found in these studies can be explained by the nature of the disease mentioned in each study. Women receive BPs treatment for conditions like osteoporosis and breast cancer, while men are treated with BPs for prostate cancer.

Study number	Type of disease	BP Type	Route and dose of administration
1	Breast cancer	Zoledronic acid	IV 4 mg every 6 months for 3 years
2	Multiple myeloma	Pamidronate	Pamidronate 30 mg: once/month for 3 years
			Pamidronate 90 mg: once/month for 3 years
3	Prostate cancer	Zoledronic acid	IV: 4 mg/4 weeks for 28.76 months
4	Cancer-free: Osteoporosis, Paget's disease	Without cancer: -Etidronate -Ibandronate	VO: less than 1 month IV: with and without cancer
	With cancer: Breast, lung, genitourinary, gastrointestinal cancer, multiple myeloma	With cancer: -Zoledronic Acid -Pamidronate	
5	Ostéoporose	Acide Zolédronique	IV: 5 mg/year
6	Osteoporosis Paget's disease	VO: -Alendronate -Residronate -Minodronate	VO: 61 month average
	Hepatocellular carcinoma Prostate cancer Multiple myeloma	IV: -Zoledronic Acid -Pamidronate -Alendronate	IV : 25 month average

Table 3: Type of bisphosphonates, dose and route of administration depending on the type of disease.

Study number	Clinical signs	Radiological signs	Onset of ONJ
1	- Fistula with purulent drainage.	-Persistence of non-remodeled bone in the extraction sites. -Thickening of Lamina Dura. - Alteration of bone trabeculation.	- 5 cases (3 mandibular and 2 in the maxilla).
2	-Tiredness. -Pain. -Bone lesions	-	-Pamidronate 30 mg: 2 cases appeared 31 to 40 months after the start of treatment. -Pamidronate 30 mg: 8 cases appeared up to 50 months after the start of treatment.
3	-	Non-healing exposed bone in mandible/ maxilla for longer than 8 weeks	40 cases
4	-	-	Without cancer: -8 cases (IV route) -0 cases (VO route)
			With cancer: -40 cases (IV route)

5	- Infection of the mucous membrane. -Aseptic bone necrosis. -Unspecified anomaly of the teeth.	- Poorly defined bone lesions.	8 cases
6	-Pain. -Mucosal inflammation. -Necrotic bone exposure.	- Lytic bone lesions.	VO: (16 mand / 12 max) -Stage 0-1: 4cases -Stage 2: 21cases -Stage 3: 2 cases
			-IV: (19 mand/12 max) - Stage 0-1: 8cases. -Stage 2: 20cases. -Stage 3: 4 cases.

Table 4: Clinical and radiological signs correlated with the occurrence of ONJ.

Oral BPs are used most often for the treatment of osteoporosis as well as other less common conditions such as Paget's disease and osteogenesis imperfecta in children. Over 190 million prescriptions for oral BPs have been dispensed worldwide [9], with Alendronate by far the most common oral BP prescribed [11]. However, IV BPs are mainly used for the treatment of tumor pathologies including breast cancer, prostate cancer, lung cancer, multiple myeloma, malignant hypercalcemia or in cases of bone metastases [11]. In 2002 the United States government identified a total of four million patients with ONJ induced by zoledronic acid [12].

Clinically ONJ associated with BPs can be asymptomatic for several weeks or even months and only be discovered in the oral cavity by baring the bone. They are usually symptomatic and painful due to infection of the soft tissue damaged by the exposed bone [13]. The intensity of the symptoms is variable and depends on the stage of development of the lesion. During the functional latency phase, ONJ can remain asymptomatic without any bone exposure or any other sign, for weeks or months (31.1% of cases according to Marx., *et al*.), Especially when the BPs are administered by VO [14-16]. It is followed by the early phase where certain signs may appear before the clinically evident appearance of osteonecrosis such as halitosis, modification of periodontal tissues, mucous ulcer not healing, mobility or loss of teeth, and inexplicable infection of soft tissue [14,15]. The status phase is the last phase where the clinical appearance can fully confirm the diagnosis of ONJ according to the classification established by AAOMS. The most characteristic aspect is the exposure in the oral cavity of a necrotic, avascularized bone of a "wet sugar" consistency, and in particular of the extraction sockets that do not heal. The patient may also describe iterative expulsions of sequesters of varying size, as well as halitosis and/or labiomental hypoaesthesia.

The use of the IV route (Zoledronic acid and Pamidronate) leads to the appearance of clinical signs and the lesions to develop faster than in the OV, which can extend to the entire jaw, which has an impact on the quality of life of patients [6,7,10].

The radiological examination is an essential tool to confirm the diagnosis of ONJ. Several techniques can be used. D. H. Solomon., *et al*. used panoramic radiography to highlight the radiological signs corresponding to stage 0 of the pathology. These are ill-defined lytic lesions of the jawbones that are difficult to detect [6,9]. For Petra Rugani., *et al*. the CT scan shows more precisely the lesion and its extent. It presents as thickening of the lamina dura, narrowing of the inferior alveolar canal, and the persistence of un-remodeled bone in the extraction sites as ill-defined irregular radiolucency (osteolysis) or a mixture of radio-clarity and radio-opacity (osteosclerosis). In two patients on IV BPs the signs were pronounced at stage 0, the CT scan showed clouding and thickening of the sinus wall [7]. Imaging techniques aimed at predicting the onset of ONJ before detecting bone exposure are yet to be established [17]. The Fasting Serum C-terminal Telopeptide (CTX) test is currently widely used for this purpose. CTX is a biological marker used to measure

the degree of bone resorption and remodeling. It can predict the development of ONJ in patients treated with BPs and thus establish an appropriate treatment plan [18-20]. According to Marx., *et al*. the rate of increase in CTX is 25.9 pg/ml per month after stopping BPs. Thus, the drug should be discontinued until the CTX level exceeds a value of 150 pg/ml [21].

Several risk factors can contribute to the onset of ONJ following administration of BPs. Certain local factors can promote the occurrence of osteonecrosis such as oral care (extractions, placement of implants, periapical and periodontal surgery involving the bone), tobacco consumption, the presence of a disease periodontal disease, or even defective oral hygiene. Infection is a classic component of ONJ. According to Thomas Mücke., *et al*. patients with a history of inflammation, dental diseases such as periodontitis and dental abscesses are 7 times more likely to develop ONJ. Poor oral hygiene promotes infection through the build-up of pathogenic bacteria that infect periodontal tissue. The healing and healing process is hampered especially with the use of BPs [18].

Systemic risk factors such as diabetes and corticosteroid consumption also promote the onset of ONJ. Corticosteroids cause a marked loss of bone mass and increase the risk of oral infections as they slow healing and alter the oral microflora [22]. Drug risk factors are linked to the direct toxicity of BPs. They are divided into two groups according to their chemical structures, first generation non-nitrogenated BPs or non-aminobisphosphonates (etidronate, clodronate, tiludronate) [13]. These BPs are rarely implicated in the occurrence of ONJ. No case of ONJ on etidronate has been confirmed to date [20]. As for nitrogenated BPs or aminobisphosphonates, administered intravenously (zoledronate, pamidronate) or orally (alendronate, risedronate, ibandronate), they are the most recent, the most powerful and the most involved in the occurrence of ONJ [23-25]. Marx reports that ONJs caused by IV BPs are more common, extensive, and difficult to treat or resolve than ONJs caused by oral BPs [3]. The use of IV BPs alone has been associated with a fairly high rate of ONJ regardless of the type of disease.

The length of exposure to treatment is probably one of the most important risk factors, the risk is even higher with the IV route [11,24,26]. According to a study carried out by Petra Rugani., *et al*. the prolonged duration and the resulting cumulative dose constitute a very important risk factor ranging from 1.5% in patients treated with IV BPs over a period of period of 4 to 12 months, 7.7% for 37 to 48 months and 11% after 4 years of treatment [18]. The results of the selected studies show that the duration of BP treatment and the resulting cumulative dose is a major risk factor for the occurrence of ONJ. The risk is all the higher with the IV route (Zoledronic acid even in reduced dose) used especially for the treatment of breast cancer in women and prostate cancer in men, due to the prolonged half-life up to 10 years [1].

Further, more in-depth analytical studies should be carried out with larger samples to minimize the margin of error.

Recommendations

Given the frequency, difficulty of management and the often reserved prognosis of ONJ, we should focus our efforts on prevention. In fact, preventing the occurrence of ONJ requires close collaboration between the attending physician (oncologist, rheumatologist, hematologist) and the dental surgeon. Several scientific societies have established recommendations for the management of patients in the absence of ONJ before, during or after treatment with BP [1].

Each patient candidate for treatment with bisphosphonates must undergo an oral examination. The objective of this assessment will be to allow the patient to begin treatment after elimination of the infectious foci. In addition, the patient will be reminded of the need for monitoring and maintaining good oral hygiene in order to reduce the risks, particularly in malignant indications where the risk is greater. After clinical and radiological examinations, if necessary a conditioning of the oral cavity should be offered. Non-conservable teeth will be extracted, waiting at least for mucosal healing before starting treatment with BP. Conservative care can be performed during treatment regardless of the indication.

The recommendations during and after treatment with BP depend on the route of administration used:

- In benign indications: Interviewing should look for additional risk factors, such as active corticosteroid therapy. If the cumulative duration of treatment does not exceed 5 years and in the absence of active corticosteroid therapy, the risk is low, all treatments are possible, including surgical, without antibiotic prophylaxis. Beyond 5 years, or in the event of association with a corticosteroid therapy or another immunosuppressive treatment, antibiotic prophylaxis should be implemented.

- In malignant indications: The risk increases with the number of injections, the attitude should be as conservative as possible. The patient is therefore followed twice a year for the duration of the treatment. All conservative treatments can be performed without special precautions. On the other hand, surgical procedures, such as implant surgery, are contraindicated and avulsions limited to teeth that cannot be kept under antibiotic coverage, until mucosal healing is achieved.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Bibliography

1. Ait Lhaj S. "Ostéonécrose des maxillaires dues aux bisphosphonates: revue systématique de littérature". *Thèse Med dent Casablanca* (2018).

2. Koth VS., *et al*. "Bisphosphonate-related osteonecrosis of the jaw: from the sine qua non condition of bone exposure to a non-exposed BRONJ entity". *Dentomaxillofacial Radiology* 45.7 (2016): 20160049.

3. Marx RE. "Reconstruction of defects caused by bisphosphonate-induced osteonecrosis of the jaws". *Journal of Oral and Maxillofacial Surgery* 67.5 (2009): 107-119.

4. Ruggiero SL., *et al*. "Bisphosphonate-related osteonecrosis of the jaw: background and guidlines for diagnosis, staging and management". *Oral Surgery, Oral Medicine, Oral Pathology, and Oral Radiology* 102.4 (2006): 433-441.

5. Mücke T., *et al*. "Prevention of Bisphosphonate-Related Osteonecrosis of the Jaws in Patients with Prostate Cancer Treated with Zoledronic acid – a prospective study over 6 years". *Journal of Cranio-Maxillo-Facial Surgery* 44.10 (2016): 1689-1693.

6. Solomon DH., *et al*. "Defining the epidemiology of bisphosphonate-associated osteonecrosis of the jaw: prior work and current challenges". *Osteoporosis International* 24 (2013): 237-244.

7. Rugani P., *et al*. "Prevalence of bisphosphonate-associated osteonecrosis of the jaw after intravenous zoledronate infusions in patients with early breast cancer". *Clinical Oral Investigations* 18.2 (2014): 401-407.

8. Goodwin JS., *et al*. "Risk of Jaw Osteonecrosis After Intravenous Bisphosphonates in Cancer Patients and Patients Without Cancer". *Mayo Clinic Proceedings* 92.1 (2017): 106-113.

9. T Shintani., *et al*. "Comparison of the prognosis of bisphosphonate-related osteonecrosis of the jaw caused by oral and intravenous bisphosphonate". *International Journal of Oral and Maxillofacial Surgery* 44.7 (2015): 840-844.

10. Gimsing P., *et al*. "Effect of pamidronate 30 mg versus 90 mg on physical function in patients with newly diagnosed multiple myeloma (Nordic Myeloma Study Group): a double-blind, randomised controlled trial". *Lancet Oncology* 11 (2010): 973-982.

11. Fonseca FP., *et al*. "Alendronate-associated osteonecrosis of the jaws: A review of the main topics". *Medicina Oral, Patologia Oral, Cirugia Bucal* 19.2 (2014): e106-111.

12. Advisory Task Force on Bisphosphonate- Related Osteonecrosis of the Jaws. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws". *Journal of Oral and Maxillofacial Surgery* 65.3 (2007): 369-376.

13. Abi Najm S., *et al*. "Osteonécrose des maxillaires chez les patients traités par bisphosphonates". *La Presse Médicale* 34 (2005): 1073-1077.

14. Ecker AW., *et al*. "Bisphosphonate-related jaw necrosis – Severe complication in maxillofacial Surgery". *Cancer Treatment Reviews* 33.1 (2007): 58-63.

15. Maes JM., *et al*. "Ostéonécrose des maxillaires sous bisphosphonates". *The Medico-Chirurgical Journal and Review Stomatologie* (2007): 1-17.

16. Srinivasan D., *et al*. "Orofacial pain – a presenting symptom of bisphosphonate associated osteonecrosis of the jaws". *British Dental Journal* 203.2 (2007): 91-92.

17. Edwards BJ., *et al*. "Updated recommendations for managing the care of patients receiving oral bisphosphonate therapy: an advisory statement from the American Dental Association Council on Scientific Affairs". *Journal of the American Dental Association* 139.12 (2008): 1674-1677.

18. Blandine R., *et al*. "Attention aux effets indésirables des bisphosphonates: ulcérartion muqueuse, retard cicatriciel et ostéonécrose. Mise au point et conduite à tenir". *Act. Odonto-Stomatol.,* 233 (2006): 7-15.

19. Hutcheson A., *et al*. "A C-terminal cross-linking telopeptide test-based protocol for patients on oral bisphosphonates requiring extraction: a prospective single-center controlled study". *Journal of Oral and Maxillofacial Surgery* 72 (2014): 1456-1462.

20. Kunchur R., *et al*. "Clinical investigation of C-terminal cross-linking telopeptide test in prevention and management of bisphosphonate-associated osteonecrosis of the jaws". *Journal of Oral and Maxillofacial Surgery* 67 (2009): 1167-1173.

21. Marx R., *et al*. "Oral bisphosphonate-induced osteonecrosis: risk factors, prediction of risk using serum CTX testing, prevention, and treatment". *Journal of Oral and Maxillofacial Surgery* 65 (2007): 2397-2410.

22. Filali S., *et al*. "Incidence, risk factors, and outcomes of osteonecrosis of the jaw: integrated analysis from three blindedactive-controlled phase III trials in cancer patients with bone metastases". *Annals of Oncology* 23.5 (2012): 1341-1347.

23. Michael M., *et al*. "Ostéonécrose maxillaire associée aux bisphosphonates: Présentation d'un cas et revue de la littérature". *Rev. Mens. Suisse Odontostomatol.,* 116.10 (2006): 1043-1047.

24. Migliorati C., *et al*. "Managing the care of patients with bisphosphonate associated osteonecrosis". *Journal of the American Dental Association* 136 (2005): 1658-1668.

25. Purcell P and Body I. "Bisphosphonates and osteonecrosis of the jaw". *Medical Journal of Australia* 182 (2005): 417-418.

26. Hoff A., *et al*. "Osteonecrosis of the jaw in patients receiving intravenous bisphosphonate therapy". *Journal of Clinical Oncology* 24 (2006): 8528.

27. Lescaille G and Baaroun V. "Conduite à tenir face à un patient traité par des inhibiteurs de la résorption osseuse à risque d'ostéonécrose des mâchoires". *Medicina Oral Patologia Oral y Cirugia Bucal* 36.2 (2019).

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