

Proposal for a preventive protocol for medication-related osteonecrosis of the jaw

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Abstract

Background: Medication-related osteonecrosis of the jaw (MRONJ) is a severe adverse reaction experienced by some patients exposed to certain drugs (antiresorptives such as bisphosphonates or denosumab, and antiangiogenic drugs). From a review of the literature it appears that there is no uniform criterion when selecting preventive measures; these vary according to author. Likewise, the measures recommended are usually general, so that in few cases they result in specific actions to be applied depending on the different variables involved such as the type of drug used, the duration of its application, the underlying pathology, the presence or absence of risk factors, etc. The aim of this study has been to design a preventive protocol which can be easily applied in any clinic or by any dental care service. **Material and Methods:** We undertook an exhaustive literature review to find any articles related to the topic of study, namely, preventive measures for medication-related osteonecrosis of the jaw, on the one hand generically and on the other focusing on dental implant treatment. The most part the criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed. From 3946 items, we selected a total of 21 items. **Results:** From the analysis of the selected articles, several protocols have been developed that are easy to apply in a dental clinic.: Protocol 1. Before starting treatment with antiresorptives (Patients who are going to be treated for osteoporosis / Patients who are going to be treated for cancer). Protocol 2. Once treatment is initiated with antiresorptives (Patients being treated for osteoporosis / Patients being treated for cancer). **Conclusions:** The application of these protocols requires an interdisciplinary team which can handle the various treatments and apply the measures contained in them. Along with a team of well-educated and trained dentists, it is equally important to maintain contact with the medical team involved in the treatment of the underlying pathology, especially rheumatologists, oncologists, internists and gynaecologists. All the above requires a great staff learning and organization effort, continuous training and coordination of the whole team involved in the preventive management of these patients.

Key words: Medication-related osteonecrosis of the jaw, clinical protocols, clinical guidelines, prevention.

Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is a severe adverse reaction experienced by some patients exposed to certain drugs (antiresorptives such as bisphosphonates or denosumab, and antiangiogenic drugs), used in cases of osteoporosis or bone manifestations in different types of cancer, to reduce skeletal complications of these conditions, achieving a reduction in pain and typical pathological fractures, as well as an improvement in the life quality of these patients (1). According to the American Association of Oral and Maxillofacial Surgeons (AAOMS 2014), patients with MRONJ should be or have been in treatment with antiresorptive or antiangiogenic drugs, present exposed bone or bone which may be probed through an intra- or extraoral fistula in the maxillofacial region, and the lesion must have persisted for more than 8 weeks with no history of radiotherapy in the region (2).

The etiopathogenesis of this type of Osteonecrosis of the Jaw (ONJ) nowadays continues to be a challenge for researchers, being a constant topic of debate. From the data available it may be deduced that the aetiology would be multifactorial, there being on the one hand inhibition of the osteoclast function by the antiresorptive drugs, which would lead to disorders in the repairing, healing and bone remodelling mechanisms, essential in protecting against infection, and microfractures which take place as a result of physiological bone function (3). On the other hand, both the antiangiogenic drugs such as Bevacizumab or Sunitinib, and some bisphosphonates such as zoledronic acid are capable of inhibiting angiogenesis, by reducing the formation of blood vessels, which is fundamental for healing and bone remodelling (4). In recent years, the infectious/inflammatory theory has become increasingly important as a cause for the emergence of ONJ. Different studies on animal models support the theory that infection or local inflammation could trigger a condition of osteonecrosis in these patients (3). Although it is well known that the majority of cases of ONJ had a dental extraction history, it is also true that normally these extracted teeth had undergone prior periodontal or periapical pathological infection, which justified their extraction. Given that most teeth with a dental inflammatory disease are eventually extracted, there may be confusion on the true role of the surgical procedure itself as a direct trigger for ONJ (2,5,6). The basic role of infection in the pathogenesis of this condition is manifested by the fact that its incidence is reduced as soon as the dental hygiene of these patients improves (7). The mechanism by which microorganisms induce ONJ could be related to the production by the bacteria in certain substances such as lipopolysaccharides which would favour reabsorption, or Receptor Activator of Nuclear Factor Kappa B Ligand (RANKL) in fibroblasts, having the same effect. Similarly, local

acidosis induced by infection has also been related as a cause of the release of bisphosphonates, facilitating osteonecrosis (8,9).

Treatment with dental implants in patients who take antiresorptives or antiangiogenic drugs has always been a controversial topic. As cases of MRONJ were being published, it was highlighted that in an elevated percentage, the precipitating factor was a dental extraction (54%-61%), such that although there was not much evidence, it was deemed that the risk of triggering an ONJ after dentoalveolar surgery would be similar to the one that existed after exodontia. In this sense, the surgical procedure of inserting an implant in these patients would involve a risk of ONJ similar to that of dental exodontia (2,10). Slowly publications began to appear which related implants with the emergence of ONJ, arousing controversy about the desirability of recommending implantological treatments in patients treated with antiresorptives, although the evidence in that respect is heterogeneous, incomplete and of low quality (11,12). There is sufficient evidence to state that the risk of implant failure due to ONJ is limited in patients undergoing treatment with antiresorptives for osteoporosis, although the risk must be assessed on an individual basis. However, in patients undergoing treatment with antiresorptives for cancer, the risk is much higher and there is a consensus that implants should be contraindicated in these cases (2,13,14).

Notwithstanding, from the evidence published in recent years, it appears that the majority of cases of peri-implant MRONJ develop as a late complication around previously osseointegrated and successfully loaded implants, such that the condition could not be attributed to the surgical procedure of implant insertion. Several publications have suggested that the presence of peri-implantitis could be a more important risk factor for MRONJ than surgical insertion, which would reinforce the importance of the infectious/inflammatory theory in the etiopathogenesis of MRONJ in these cases (14-18). Treatment of MRONJ once established is complex, because it depends on the stage of the disease, there being several therapeutic approaches, sometimes conflicting, depending on the authors undertaking it. Bermúdez *et al.* (19) carried out a study on the different therapeutic approaches found in the literature and grouped them into seven protocols, each one of which covered different types of treatment, highlighting that the best results were obtained with a conservative protocol, with clinical and radiological follow-up, minimally invasive surgical treatment and various adjuvant measures. This shows the enormous variety of existing proposals and the difficulty in tackling the process therapeutically. In part due to the above, when talking of therapeutic management of these patients, stress has been laid on the importance of a multi-disciplinary approach which

should include consulting qualified dental professionals, when deciding on treating a patient with antiresorptives or antiangiogenics. There is increasing evidence that early screening, the application of adequate preventive measures and correct dental care before initiating antiresorptive treatment, achieve a reduction in the incidence of MRONJ using guidelines covering educational aspects and ones aimed at motivating patients to take part in their dental healthcare, as well as measures targeted at eliminating or preventing infected dental, periodontal and peri-implant sites (2,10,20-22). Likewise, preventive protocols for performing surgical extractions with the least possible trauma have been described, using antibiotic prophylaxis, finding a reduction in the risk of osteonecrosis (23,24).

However, from a review of the literature it appears that there is no uniform criterion when selecting preventive measures; these vary according to author. Likewise, the measures recommended are usually general, so that in few cases they result in specific actions to be applied depending on the different variables involved such as the type of drug used, the duration of its application, the underlying pathology, the presence or absence of risk factors, etc. A similar situation arises with follow-up times, when check-ups should be carried out, or with the drugs and preventive measures employed before an exodontia or any other surgical procedure in these patients.

We have not found in the literature any clearly defined, wide-ranging protocol which outlines specifically and systematically the different preventive measures for MRONJ set out in published studies in the literature, and especially for patients who are carriers or who wish to receive treatment with dental implants. Therefore, the aim of this study has been to design a preventive protocol which can be easily applied in any clinic or by any dental care service; one which is systematic and detailed and which takes into consideration all the variables involved in those patients who have received or are receiving treatment with antiresorptive or antiangiogenic drugs, and who are wearers or are about to receive treatment with dental implants.

Material and Methods

- Protocols and eligibility criteria

We undertook an exhaustive literature review to find any articles related to the topic of study, namely, preventive measures for medication-related osteonecrosis of the jaw, on the one hand generically and on the other focusing on dental implant treatment. Although for the most part the criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed, this review cannot be considered strictly systematic, due to the large number of variables involved in the search, given that our aim was to draw up a preventive protocol describing all the mea-

asures published in the literature. As a result of the huge spread of the data in the published articles and the heterogeneous nature of these, we deemed it inappropriate to ask a specific PICO question because we ran the risk of leaving out articles relevant to our search. For this reason, likewise, we had to resort to review or expert opinion articles, which placed more emphasis on the specific preventive measures we wished to include in the protocol.

The inclusion criteria were: (a) Studies published between January 2003 and 30 January 2019; (b) Human studies; (c) Any language; (d) case series, cohort studies, case-control studies, and controlled and/or randomized controlled clinical trials (CTs/RCTs); (e) retro or prospective studies; (f) studies including patients having undergone or undergoing oral or parenteral antiresorptive or antiangiogenic drugs, with or without implant treatment, to whom any type of protocol or preventive measure was being applied; (g) review articles, systematic reviews and meta-analysis on the application of preventive measures or protocols for MRONJ in patients having taken, taking or planning to take the drugs involved. The following exclusion criteria were applied: (a) that they did not meet the inclusion criteria; (b) animal studies; (c) case reports.

- Search sources and strategy

An electronic search was conducted using three databases, PubMed, (Medline), Embase (Ovid) and Cochrane database of systematic reviews. The review was completed with a manual search in scientific journals in this sector in the e-library of the University of Seville. Likewise lists of references in all the publications identified were reviewed.

Search of the Medline (PubMed) database was carried out using MeSH (Medical Subjects Headings) terms and free terms, in different combinations using Boolean Operators "AND" and "OR". The terms used were general terms; ("Dental" OR "Oral"). Terms related to drugs involved; ("Diphosphonates" OR "Bisphosphonates" OR "Alendronic Acid" OR "Alendronate" OR "Etidronic Acid" OR "Etidronate" OR "Ibandronic Acid" OR "Ibandronate" OR "Pamidronate" OR "Risendronic Acid" OR "Risedronate" OR "Zoledronic Acid" OR "Zoledronate" OR "Denosumab" OR "Human monoclonal antibody to RANKL" OR "RANK ligand" OR "RANK antibody" OR "Bevacizumab" or "Sunitinib" OR "Antiresorptive drugs" OR "Antiresorptive agents" OR "Angiogenesis inhibitor". Terms related to Osteonecrosis of the jaw; "Bisphosphonate-associated osteonecrosis of the jaw" OR "Medication related osteonecrosis of the jaw" OR "Jaw osteonecrosis" OR "Osteonecrosis" OR "MRONJ" OR "BRONJ". Terms related to dental implants; "Dental implants" OR "Dental implant" OR "Dental implants adverse effects" OR "Implant treatment" OR "Implant therapy" OR "Implants" OR

“Osseointegration” OR “Osseointegrated dental implantation” OR “Dental implantation, endosseus” OR “Implant loss” OR “Implant failure” OR “Periimplantitis” OR “Peri-implantitis” OR “Periimplant disease” OR “. Terms related to dental extraction or oral surgery as a risk factor; “Tooth extraction” OR “Tooth extractions” OR “Dental extraction” OR “Oral surgery” OR “Oral surgery procedure” OR “Oral surgery procedures” OR “Procedures, oral surgery”. Terms related to prevention or preventive measures for osteonecrosis; “Preventive dentistry” OR “Prophylaxis” OR “Dental Prophylaxis” OR “Prophylaxis, dental” OR “Preventive measures” OR “Preventive management” OR “Antibiotic Prophylaxis” OR “Antibiotic” OR “Bisphosphonates-associated osteonecrosis of the jaw therapy” OR “Bisphosphonates-associated osteonecrosis of the jaw prevention and control” OR “Bisphosphonates-associated osteonecrosis of the jaw preventive protocol” OR ”Preventive protocol” OR “Preventive” OR “Protocol”. For the other two databases, similar terms were used but adapted to the specific criteria of each of them.

- Data gathering and extraction

Two authors (MMRR and MRS) reviewed all the titles and abstracts independently. After ruling out all those which did not meet the eligibility criteria, the complete

text of the remaining articles was reviewed. The complete text of those which offered little information in the title or abstract were also selected, to avoid missing out any relevant article. Any disagreements were resolved by discussion between the two reviewers.

Results

- Articles selected

Fig. 1 shows the flowchart of the search process. Of the 3946 initial articles, after the various exclusion processes, 21 articles were selected which met the inclusion criteria. The articles included were grouped into: clinical articles (n=10, Table 1); (Dimopoulos *et al.*, 2009 (20); Ripamonti *et al.*, 2009 (25); Lodi *et al.*, 2010 (26); Fertito *et al.*, 2011 (27); Kwon *et al.*, 2012 (28); Vandone *et al.*, 2012 (29); Bramati *et al.*, 2014 (30); Troeltzsch *et al.*, 2016 (31); Giovannacci *et al.*, 2016 (13); Mücke *et al.*, 2016 (32)). Review articles on MRONJ (n=6, Table 2); (Ruggiero *et al.*, 2014 (2); Otto *et al.*, 2015 (33); Diniz-Freitas *et al.* 2016 (34); Beth-Tasgodan *et al.*, 2017 (35); Di Fede *et al.*, 2018 (36); Karna *et al.*, 2018 (37)). Review articles on relation between MRONJ and dental implants (n=5, Table 3); (Ata-Ali *et al.*, 2016 (11); Freitas *et al.*, 2016 (38); Walter *et al.*, 2016 (18); Guazzo *et al.*, 2017 (39); Stavropoulos *et al.*, 2018 (1)).

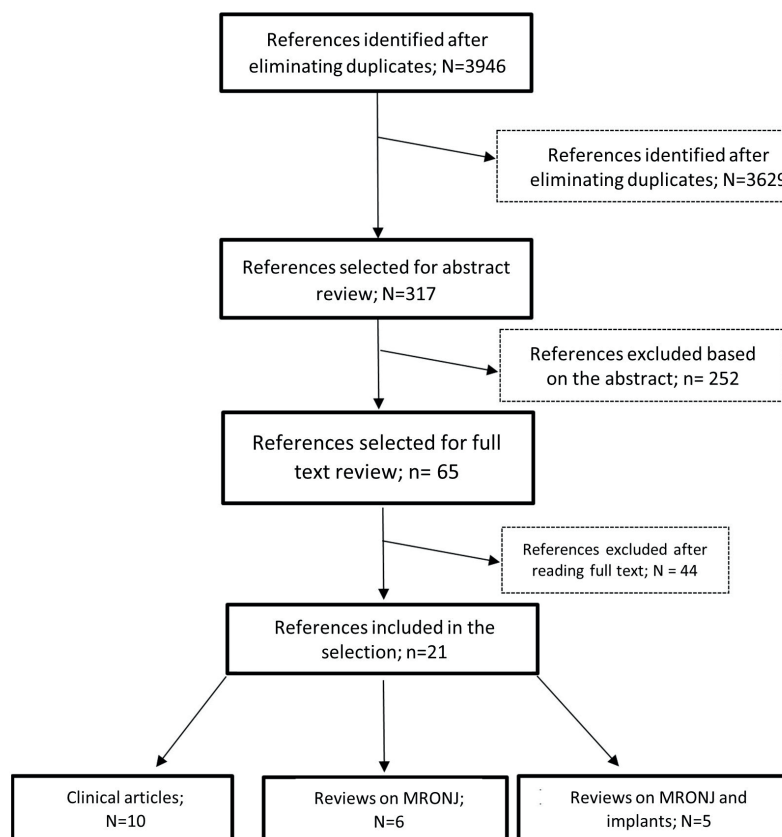


Fig. 1: Flowchart of the search and inclusion process for studies for review.

Table 1: Clinical articles.

article	N	procedure	underlying disease	medication	administration route	treatment	follow-up	incidence	type of study	conclusions
Dimopoulos <i>et al</i> , Ann Oncol. 2009. (20)	128	group A (38) and B (90) if treatment was initiated before or after implementation of the preventive measures.	cancer (multiple myeloma)	bisphosphonates (zoledronate)	intravenous	extraction, implant or spontaneous	2.5 to 55 months	16 patients (12.5%) developed ONJ: 10 in group A (26.3%) and 6 in group B (6.7%)	prospective and retrospective	The risk of developing ONJ after treatment with zoledronic acid is reduced (but not eliminated) by the implementation of preventive measures.
Ripamonti <i>et al</i> , Annals of Oncology. 2009. (25)	966	patients undergoing oral reviews to detect possible dental disorders and dental care if necessary, thus estimating incidence of ONJ	903 cancer, 27 osteoporosis, 36 both	bisphosphonates (zoledronate, pamidronate, clodronate)	oral and intravenous	prevention	6 years retrospective and 2 years prospective	ONJ went from 3.2% to 1.3% after applying prevention	prospective and retrospective	There is an important reduction in ONJ in those patients receiving suitable preventive dental measures.
Lodi <i>et al</i> , J Oral Maxillofac Surg. 2010 (26)	38 extractions	protocol to reduce the risk of ONJ, based on controlling local and systemic infection using chemical and mechanical reduction of local bacterial load and antibiotic prophylaxis.	21 cancer and 2 osteoporosis	bisphosphonates (zoledronate, pamidronate, clodronate)	intravenous	extraction	1 year	0% developed ONJ	prospective	The proposed preventive protocol seems to reduce the risk of ONJ after dental extraction in a group of subjects treated with intravenous bisphosphonates.
Ferlito <i>et al</i> , J Oral Maxillofac Surg. 2011 (27)	102 extractions	preventive protocol for patients receiving zoledronate and requiring simple or multiple dental extractions	cancer	bisphosphonates (zoledronate)	intravenous	extraction	12 months	0% developed ONJ	Uncontrolled longitudinal observational.	extraction of alveolar bone after extraction of teeth and correct antimicrobial prophylaxis
Kwon <i>et al</i> , Clin Oral Implants Res. 2012 (28)	19	analysis of clinical, radiological and histological findings in patients diagnosed and treated for ONJ associated with implant placement	osteoporosis	bisphosphonates	oral and intravenous	implants	3 years	3 patients developed ONJ after implant placement and 9 patients developed ONJ on average within 35 months.	prospective	already osseointegrated dental implants may also cause osteonecrosis
Vandone <i>et al</i> , Ann Oncol. 2012 (29)	269	comparison between a retrospective group without prevention and a prospective group with prevention	cancer	bisphosphonates (zoledronate, pamidronate)	intravenous	prevention	47 months	ONJ went from 5.5% to 2.8% after applying prevention	prospective and retrospective	implementation of a preventive dental programme can reduce the risk of ONJ in metastatic patients treated with i.v.
Bramati <i>et al</i> , J Bone Miner Metab. 2015 (30)	212	Strict prevention programme and comparison with a prior cohort study without dental prevention	cancer	bisphosphonates (zoledronate, pamidronate)	Intravenous	prevention	5 years	100% efficient prevention	prospective	ONJ could be effectively prevented. Recommendation of an obligatory preventive programme including a multidisciplinary team for all patients starting BP.
Troeltzsch <i>et al</i> , J Craniomaxillofac Surg. 2016 (31)	117	analyses of peri-implant parameters are associated with peri-implant ONJ.	29 cancer, 5 osteoporosis	bisphosphonates or denosumab	oral and intravenous	Implants	6 years	ONJ 44%. Signs of peri-implantitis (39%): seemed to be associated with ONJ.	retrospective	Patients receiving high doses of antiresorptives have risk of developing peri-implant ONJ
Giovanacci <i>et al</i> , J Craniofac Surg. 2016 (13)	15	G1: necrosis immediately after placement of the implant (from 2 to 10 months). G2: distant necrosis (from 1 to 15 years)	9 cancer and 6 osteoporosis	bisphosphonates (alendronate, ibandronate, zoledronate)	oral and intravenous	implants	15 years	**	retrospective	information to patients taking BP and wanting placement of IOI; but also those going to start treatment with BP and have IOI
Mücke <i>et al</i> , J Craniomaxillofac Surg. 2016 (32)	253	Group A monitored and treated when the dentist deemed it necessary and was reassessed once a year. Group B, patients monitored and treated by the authors when necessary at 12-week intervals.	cancer (prostate metastasis)	bisphosphonates (zoledronate)	intravenous	prevention	between 1 and 7 years	22.3% ONJ in control group and 2.2% ONJ in study group	prospective	Preventive oral and maxillofacial treatment before the application of bisphosphonate combined with dental follow-ups at 3 months significantly reduces the emergence and risk of ONJ

Table 2: Review articles on osteonecrosis.

Article	no. articles reviewed	type of articles reviewed	key words	aims	conclusions
Ruggiero <i>et al</i> , J Oral Maxillofac Surg. 2014 (2)	184	Controlled clinical trials, cases and controls, ECA and cohorts.	X	1. Estimates of risk of ONJ. 2. Comparisons of risks and benefits of drugs related to ONJ to facilitate decision making. 3. Guidance to clinics on: a. differential diagnosis of ONJ in patients with a history of exposure to antiresorptive and / or antiangiogenic agents. b. Prevention measures and management strategies for ONJ.	The Special Committee recommends changing the nomenclature of bisphosphonate-related osteonecrosis of the jaw. The Special Committee favours the term medication-related osteonecrosis of the jaw.
Otto <i>et al</i> , J Craniomaxillofac Surg. 2018 (33)	30	Prospective and retrospective	Bisphosphonates, Bisphosphonate-related osteonecrosis of the jaw, Medication-related osteonecrosis of the jaw, MRONJ, Prophylaxis, Risk factors, Tooth extractions	To investigate the result of tooth extractions in patients receiving bisphosphonate therapy.	Tooth extraction can be performed safely and predictably, even in high risk patients, when it is undertaken in accordance with established guidelines. It is not tooth extraction itself but rather the prevailing infectious conditions which may be a key risk factor for the development of ONJ.
Diniz-Freitas <i>et al</i> , Med Oral Patol Oral Cir Bucal. 2016 (34)	13	Systematic review and meta-analysis	Bisphosphonates, angiogenesis inhibitors, antiresorptive drugs, extraction, osteonecrosis.	To identify the most relevant protocols and the best measures for preventing ONJ secondary to dental extraction.	no scientific evidence is available on the effectiveness of prevention protocols for ONJ in patients treated with antiresorptive or antiangiogenic drugs who undergo dental extraction.
Beth-Tasdogan <i>et al</i> , Cochrane library. 2017(35)	5	Randomized controlled trials	X	1. To assess the effects of operations vs. no treatment, placebo or active control for prophylaxis of ONJ in patients exposed to antiresorptive or antiangiogenic drugs. 2. To assess the effects of non-surgical or surgical procedures vs. no treatment, placebo or active control for the treatment of persons with ONJ.	Dental examinations at three monthly intervals and preventive treatments can be more effective than standard care for reducing the incidence of ONJ. The certainty of the evidence was assessed as low. There are insufficient tests to claim or refute a benefit from operations tested for ONJ prophylaxis
Di Fede <i>et al</i> , Biomed Res Int. 2018 (36)	64	descriptive	X	To describe the new paradigm on preventive dental management in patients at risk of ONJ, before and during / after the administration of medication	The need for a standardized multidisciplinary approach, with sustained dialogue between specialists, to improve the effectiveness of preventive strategies and enhance patient quality of life.
Karna <i>et al</i> , J Oral Oncol. 2018 (37)	6	Controlled clinical trials, cases and controls, ECA and cohorts.	X	To assess the effectiveness of dental procedures to prevent or reduce the incidence of ONJ in patients with cancer receiving antiresorptive treatment, compared to similar control groups not receiving any procedures	No conclusive proof was evinced. Therefore, further large-scale prospective studies are required with well-defined procedures and control groups, and consistent measurement of results in both groups.

Table 3: Review articles on osteonecrosis and implants.

Article	No. articles reviewed	Type of articles reviewed	Key words	Aims	Conclusions
Ata-Ali <i>et al</i> , Clin Oral Implant Res. 2014 (11)	15	(i) Studies including patients with a history of systemic BP therapy (via the oral and/or intravenous route) and receiving at least one dental implant before or after BP administration; (ii) Prospective or retrospective studies and cases series; (iii) Studies specifying implant success rate.	Dental implants, bisphosphonate(s), etidronate, clodronate, risedronate, alendronate, ibandronate, pamidronate, zoledronic acid.	To assess the scientific evidence that bisphosphonate therapy can reduce the success rate of dental implants.	Placement of dental implants in patients receiving bisphosphonates does not reduce the success rate of dental implants. These patients are not exempt from complications and, therefore, risk assessment must be established on an individual basis
De Freitas <i>et al</i> , Med Oral Patol Oral Cir Bucal. 2016 (38)	15	Articles included in patients undergoing bisphosphonate therapy (oral and intravenous) and undergoing dental implant procedure; cases series; retrospective studies; prospective studies.	Bisphosphonates, diphosphonates, dental implants, osteonecrosis.	To analyse articles studying patients who underwent bisphosphonate therapy and receiving dental implants before, during or after bisphosphonate treatment.	Care must be taken when planning dental implant surgery in patients receiving bisphosphonate treatment due to the risk of developing ONJ and implant failure. Furthermore, the overall systemic condition of the patient should be taken into consideration when undertaking such procedures.
Walter <i>et al</i> , Int J Implant Dent. 2016 (18)	50	Prospective (controlled randomized, non-randomized controlled studies, cohort studies) and retrospective (control, case control, single cohort) and case series treating dental implants in patients with antiresorptive therapy.	Bisphosphonate associated osteonecrosis of the jaw, Bisphosphonate, Dental implant, Denture, Augmentation, Sinus lift, Antibiotics, Quality of life	To ascertain which patients with antiresorptive therapy (BP, denosumab) benefit from dental implants without being exposed to an unreasonably high risk of developing osteonecrosis.	Successful implant therapy is possible in patients receiving antiresorptive therapy. The possibility of developing osteonecrosis should be explained to the patient. Individual risk assessment is essential, bearing in mind the primary disease with the medication and other diseases and medications which compromise wound healing. Whenever possible, bone augmentation should be avoided, and in these patients perioperative antimicrobial prophylaxis is recommended.
Guazzo <i>et al</i> , J Oral Implant 2017(39)	10	Retrospective studies, cross-sectional studies and prospective studies	antiresorptive drugs, bisphosphonates, dental implants, implant failure, ONJ	To assess the scientific literature relating to implant placement in users of antiresorptive agents and the risk related to implant failure and the development of ONJ.	Antiresorptive therapy must be considered a risk factor until further prospective testing is carried out.
Stavropoulos <i>et al</i> Clin Oral Implants Res. 2018 (1)	36	Case series, cohort studies, case-control studies, and controlled and/or randomized controlled clinical trials; retro- or prospective design; and ≥ 10 patients with systemic intake of ARDs	Antiresorptive drugs, bisphosphonates, dental implants, hormone replacement therapy, medication-related osteonecrosis of the jaw, systematic review	To assess the possible side effects of taking antiresorptive drugs in relation to various aspects of implant therapy	Taking low-dosage oral bisphosphonates for the treatment of osteoporosis, in general, does not compromise implant therapy. There is almost no information available about the possible effect on implant therapy of high dosages, or the success or safety of bone graft procedures.

- Preventive protocols

The different variables involved were grouped into two preventive protocols; one for patients who had not yet begun treatment with antiresorptive drugs and the other for those who were already being treated with said drugs. Each group comprised in turn two subgroups depending on whether they were patients treated for osteoporosis or for cancer.

Protocols, for patients already treated or who wished to be treated with dental implants, are outlined below.

PROTOCOL 1. BEFORE STARTING TREATMENT WITH ANTIRESORPTIVES (Fig. 2)

A. PATIENTS WHO ARE GOING TO BE TREATED FOR OSTEOPOROSIS.

B. PATIENTS WHO ARE GOING TO BE TREATED FOR CANCER.

PROTOCOL 2. ONCE TREATMENT IS INITIATED WITH ANTIRESORPTIVES (Fig. 3)

A. PATIENTS BEING TREATED FOR OSTEOPOROSIS

B. PATIENTS BEING TREATED FOR CANCER

PROTOCOL 1.A. PATIENTS WITH OSTEOPOROSIS BEFORE INITIATING ANTIRESORPTIVE TREATMENT							
	A. INFORMATION AND PREVENTIVE GUIDANCE MEASURES (Common to all protocols)	B. PREVENTIVE MEASURES INDICATED AFTER CLINICAL AND RADIOLOGICAL EXAMINATION OF THE MOUTH	C. FEASIBLE TREATMENTS	D. CONTRAINDICATED TREATMENTS	E. RISK FACTOR CONTROL	F. PREVENTIVE FOLLOW-UP	G. MEASURES BEFORE PLACEMENT OF AN IMPLANT OR ANY OTHER TYPE OF SURGERY
1	Basic information about ONJ and its risk factors	Initial panoramic radiography, besides apical or blowing radiographs if required.	Orthodontic treatment	In these patients there are NO contraindicated treatments.	Associate antiresorptive or antiangiogenic drugs.	It will start once treatment is initiated, Protocol 2A being applied.	Proceed in a similar fashion to any other patient who does not take these drugs.
2	Information about when and at what percentage the risk of ONJ will begin in your specific case.	Scaling and oral hygiene education: brushing technique, management of interdental brushes, floss and maintenance mouthwashes, to obtain excellent oral healthcare.	Conventional prosthetic treatment		Taking corticosteroids.		
3	Information about implant treatment: surgery and infection as risk factors of ONJ.	Exhaustive cleaning of the prosthesis on dental implants, dismantling them on hygiene day, if possible, and maintenance hygiene technique education: brushes, mouthwashes, interdental brushes, irrigators, etc.	Implantological treatment and related surgery (GBR, sinus lift, connective tissue grafts, removal of teeth included, etc.)		History of radiotherapy in the year prior to initiation of treatment		
4	Information about the need to maintain excellent oral hygiene in general and of implants in particular.	Non-restorable tooth extraction or with a poor restorative prognosis (whose medium-term maintenance in the mouth cannot be guaranteed).	Tooth rescue surgery including for orthodontic treatment		Habitual drinking of alcohol (men >4 standard units per day, women >2 units/day)* * a standard unit = 10g of alcohol, * 10 g of alcohol = 100cc of wine, 200cc of beer or 25 cc of spirits		
5	Need for regular visits for the detection and elimination of any site of infection in the mouth in general and around implants in particular.	Fill any tooth decay with a good restorative prognosis.	Other similar surgical techniques		Smoking above 8-10 cigarettes a day		
6	Explanation of ONJ symptoms so as to immediately attend the clinic when faced with the slightest suspicion.	Endodontic treatment of any tooth requiring it and which has a good restorative prognosis.					
7		Periodontal treatment in patients with pockets larger than 4 mm					
8		Peri-implant mucositis treatment. If there is any peri-implantitis site, treat it or extract the implant if regenerative treatment is not possible.					
9		Performance of any surgical procedure needed to eliminate infection sites or prevention of sites and future complications: periodontal surgery, periapical surgery, surgery for retention, cysts, tumours, etc.					
10		If you are a removable prosthesis wearer, make an adjustment to it, removing decubitus ulcers, or providing a new one if the old one cannot be adjusted.					

PROTOCOL 1.B. PATIENTS WITH CANCER BEFORE INITIATING ANTIRESORPTIVE TREATMENT							
1	(Identical to Protocol 1A)	(Identical to Protocol 1A)	Orthodontic treatment	* Implantological treatment and related surgery (GBR, sinus lift, connective tissue grafts, removal of teeth included, etc.) * Any other surgery whose aim is not the elimination of infectious sites.	(Identical to Protocol 1A)	It will start once treatment is initiated, Protocol 2B being applied.	* In these patients, implant placement or any other surgery whose aim is not the elimination of infectious sites is CONTRAINDICATED. * Faced with any necessary surgery, reduce bone handling and ensure first intent closure. * Faced with any necessary surgery, wait to start treatment at least until mucosal closure of the wound (4-6 weeks)
2			Conventional prosthetic treatment				

CONSIDERATIONS FOR PROTOCOL 1A

- Although the risk of ONJ in these patients starts in the fourth year after treatment, initial measures (B) should be applied as soon as possible to introduce the patient into the oral health culture and absence of infection.
- It must be noted that the placement or presence of dental implants carries an indefinite long-term risk, although in these patients it is extremely low and begins in the 4th year after treatment.
- Provide the patient with exhaustive information about every procedure to be followed and undertake detailed informed consent.

CONSIDERATIONS FOR PROTOCOL 1B

- If medically possible, implement initial measures (B) BEFORE INITIATING THE TREATMENT. Otherwise, do so as soon as possible by taking the proper measures. (Apply Protocol 2B)
- Be aware that the presence of dental implants carries a risk of indefinite long-term ONJ, greater than that of patients with osteoporosis, therefore it is essential to prevent peri-implantitis through good hygiene and professional follow-up (follow Protocol 2B after initiating the treatment).
- Provide the patient with exhaustive information about every procedure to be followed and undertake detailed informed consent.



Fig. 2: Protocols 1A and 1B.

A. INFORMATION AND PREVENTIVE MEASURES		B. PREVENTIVE MEASURES INDICATED AFTER CLINICAL AND RADIOLOGICAL EXAMINATION OF THE MOUTH		C. FEASIBLE TREATMENTS		D. CONTRAINDICATED TREATMENTS		E. RISK FACTOR CONTROL	F. PREVENTIVE FOLLOW-UP	G. MEASURES BEFORE PLACEMENT OF AN IMPLANT OR ANY OTHER TYPE OF SURGERY
<p>PROTOCOL 2.A. PATIENTS WITH OSTEOPOROSIS ONCE ANTIRESORPTIVE TREATMENT HAS BEEN INITIATED</p> <p>In this protocol patients are divided into two groups, irrespective of the drug and administration route used: * LOW RISK GROUP (LRG): patients undergoing treatment for less than 3 years and with no associated risk factor. They will be treated the same as patients with osteoporosis before initiating treatment (Protocol 1A) * HIGH RISK GROUP (HRG): patients undergoing treatment for more than 3 years, or those who have been treated for less than three years but present other risk factors.</p>										
1	Identical to Protocol 1A	Identical to Protocol 1A except points 4, 7, 8 and 9 in which the following shall be implemented: * LRG patients: do not require specific measures. * HRG patients: apply Section G measures	LRG patients may receive any orthodontological or surgical technique without applying specific medical or surgical protocols, before going into the HRG. The following may be undertaken: Orthodontic treatment	HRG patients: The following may be undertaken: Orthodontic treatment	Conventional prosthetic treatment	Implantological treatments, related surgery (ISR, sinus lift, connective tissue grafts, elimination of both infected, etc.), or any surgical treatment, but APFC/ONS Section G PROTOCOL	LRG: Warn of implant failure risk or long-term ONJ. HRG: Warn of short-, mid- and long-term risk of ONJ.	Identical to Protocol 1A	<p>Clinical examination:</p> <ul style="list-style-type: none"> LRG: Annual HRG: Every 6 months <p>The following will be carried out: * Detection of new tooth decay. * New periodontogram * Look for signs of mucositis and/or periodontitis. * Periapical radiography if there is periapical pathology > 5 mm * LRG: Annual * HRG: Every 6 months</p>	<p>ONLY FOR HRG PATIENTS</p> <p>Prior to the procedure:</p> <ul style="list-style-type: none"> * Rinse with mouthwash containing 0.12% Chlorhexidine three times a day, 7 days before. * Administration of 850/125 mg Amoxicillin/Clavulanic Acid three times a day (one hour before the procedure and up to at least one week after, if allergic to penicillins, administer 300 mg Clindamycin three times a day, same guideline).
2			Conventional prosthetic treatment	Conventional prosthetic treatment	Conventional prosthetic treatment				<p>Scaling:</p> <ul style="list-style-type: none"> LRG: simple annual the first three years and every 6 months from year four. HRG: Every 6 months. Special emphasis on post-implant maintenance. 	<p>During the procedure:</p> <ul style="list-style-type: none"> * Always perform, including extractions, a total thickness flap enabling subsequent primary closure of the wound, if necessary, carrying out adequately. Smooth the sharp bone rim drill bit and bone file. * If several extractions are required, do them one at a time. * Use surgical ultrasound for bone handling if possible. * Meticulous stitching of the wound without tension.
3									<p>Paranasal radiography and CBCT:</p> <ul style="list-style-type: none"> Look for radiological signs of any type of infection including post-implants, or signs of ONJ. LRG: Annual HRG: Every 6 months 	<p>After the procedure:</p> <ul style="list-style-type: none"> * Rinse with mouthwash containing 0.12% Chlorhexidine three times a day, for 15 days. Gel with the same concentration may likewise be used. * After surgery do not wear removable dentures for at least the next three weeks. * Review of the wound after 3, 6 and 12 months the first year.
4	<p>CONSIDERATIONS FOR PROTOCOL 2A</p> <ul style="list-style-type: none"> * ONJ risk begins four years after treatment, or before if there are risk factors; apply the measures as soon as possible to introduce the patient into the oral healthcare culture and the absence of infection, and always prior to said decision date. * Assess the benefit to risk ratio on an individual basis and, in consultation with the patient, take the decision to undertake any surgical procedure. * Provide the patient with detailed information about every measure to be taken and obtain a signed detailed informed consent form. * If it is necessary to carry out surgery on a patient being treated with Denosumab, it is advisable to do so between the first and third month after taking the last dose of the drug, so that there is time for the soft tissues to heal before the following dose, its latency period being 6 months. 							<p>Reinforce preventive information and guidelines (Point A): Every 6 months</p>	<p>Therapeutic Drug Holiday</p> <ul style="list-style-type: none"> * Ask the doctor to change about the possibility of interrupting administration of the drug temporarily until after the surgical procedure and resuming it some time later, replacing it or not with another drug during this period. Indication of this therapeutic holiday will vary depending on the drug and the underlying disease: LRG: Do not require the drug to be withdrawn given the low risk of ONJ. HRG: If possible, a therapeutic drug holiday may be initiated suspending it for two months before the procedure and resuming it when the measure has healed completely. In the case of taking Denosumab an interruption is not required. 	
5									<p>Lower NaF/VO or sublingual patient concentrates (PROF or L-PROF)</p> <ul style="list-style-type: none"> * In these patients, the risk of ONJ could be reduced with these treatments. 	
<p>PROTOCOL 2.B. PATIENTS WITH CANCER ONCE ANTIRESORPTIVE TREATMENT HAS BEEN INITIATED</p>										
1	Identical to Protocol 1A	Identical to Protocol 1A except points 4, 7, 8 and 9 (extractions, periodontal treatment, peri-implantitis and surgical treatment of infectious sites) in which measures from Section G shall be applied	Orthodontic treatment	Any surgical treatment not aimed at eliminating infectious sites.			Identical to Protocol 1A	<p>Clinical examination:</p> <ul style="list-style-type: none"> To be carried out every 6 months. * Detection of new tooth decay. * New periodontogram * Probing of implants in search of signs of peri-implantitis. * Periapical radiography if there is periapical pathology > 5 mm periapical pathology * Clinical examination looking for signs of ONJ 	Identical to Protocol 2.A. HRG patients	
2			Conventional prosthetic treatment					<p>Scaling and non-surgical periodontal treatment:</p> <ul style="list-style-type: none"> Every 4-6 months, depending on patient response. Special emphasis on post-implant maintenance. 	Identical to Protocol 2.A. HRG patients	
3								<p>Paranasal radiography every 6 months and annual CBCT:</p> <ul style="list-style-type: none"> Look for radiological signs of any type of infection including post-implants, or signs of ONJ. 	Identical to Protocol 2.A. HRG patients	
4	<p>CONSIDERATIONS FOR PROTOCOL 2B</p> <ul style="list-style-type: none"> * Warn from the outset that the presence of dental implants prior to treatment carry an indefinite risk. Prevention and early detection of symptoms of peri-implantitis are essential. * Provide the patient with exhaustive information about every procedure to be carried out and obtain a signed consent form. * Given the risk described of a resurgence of fractures on withdrawing Denosumab, caution must be exercised with the drug holiday for this drug and always under the supervision of the doctor in charge. If it is necessary to carry out surgery on a patient being treated with Denosumab, it is advisable to do so between the first and third month after taking the last dose of the drug, so that there is time for the soft tissues to heal before the following dose, its latency period being 6 months. 							<p>Reinforce preventive guidance and information (Point A): Every 6 months.</p>	<p>Therapeutic Drug Holiday</p> <ul style="list-style-type: none"> * Ask the doctor to change about the possibility of interrupting administration of the drug temporarily until after the surgical procedure and resuming it some time later, replacing it or not with another drug during this period. Indication of this therapeutic holiday will vary depending on the drug * For patients being treated with Bisphosphonates or antiangiogenics except Denosumab, withdraw at least one week before and resume 4-6 weeks afterwards. * For patients being treated with Denosumab, withdraw at least 6-7 weeks before and resume 4-6 weeks afterwards. 	
5									Identical to Protocol 2.A. HRG patients	

Fig. 3: Protocols 2A and 2B.

Discussion

Antiresorptive drugs have begun to cover an important therapeutic field in two broad groups of patients, those affected by osteoporosis from various sources and those who suffer from oncological osteolytic processes. These conditions have in common the loss of bone density and the possibility of pathological fractures emerging which considerably compromise quality of life and entail high morbidity and elevated therapeutic costs, amongst other problems. These drugs have demonstrated their capacity for reducing bone symptoms although in certain cases they can induce osteonecrotic lesions of the jaw as an undesired effect of their use, possibly leading to serious consequences for the patient (2). Even though the risk of suffering an ONJ in patients with osteoporosis is very low (between 0.1 and 0.21 according to different series), in recent years alerts have been raised about how misleading this data is, since the number of persons undergoing treatment for osteoporosis is very elevated, it is a chronic treatment, and the risk of ONJ increases over the time the drug is taken, these being reasons why some authors point to the frequency of ONJ in these patients being greater than initially suspected (33). Warnings have been issued about

the fact that many patients treated with antiresorptives for osteoporosis, do not meet the criteria established for prescribing said medication, which is why the prevention of ONJ should start by unifying criteria across different medical professionals for proper prescription of the drugs which produce it and thus avoid cases of unnecessary treatment. Otherwise, the risk of ONJ in patients with certain cancers is much greater (0.7% - 7.7 % according to series) so although it is advisable to apply preventive measures in all cases, in these patients it is important to maximize them. Etiopathogenetic mechanisms are still controversial, different etiopathogenetic theories having been postulated to explain the emergence of ONJ (9,34). It is clear that dentoalveolar surgery involves an aggression to a bone depleted of its remodelling functions by the lack of osteoclasts, which would prevent it from coping with demands, which together with antiangiogenesis caused by drugs could justify osteonecrosis. However, data exist that contradict this theory such as the fact that the significant reduction in osteoclastic activity mediated by these drugs would induce a predominance of osteoblastic activity and therefore would lead more towards osteopetrosis than towards osteonecrosis. Likewise, in

conditions such as hyperparathyroidism in which bone turnover is also reduced, osteonecrosis does not occur, however there are patients described with ONJ in which said turnover is normal (7,31). In this context, ever more data reinforce the role of infectious-inflammatory processes in the development of osteonecrosis, which is manifested in the significant decrease in the incidence of ONJ reported by many authors in patients to whom preventive measures are applied aimed at improving oral hygiene and reducing infectious processes in these patients (20,25-30). These data justify of themselves the need for applying preventive measures for infectious-inflammatory conditions in these patients as part of their therapeutic management and manifest the importance of having systematic protocols which can be routinely applied to these patients.

It has been suggested that microorganisms could induce bone resorption in ONJ by producing certain substances such as lipopolysaccharides which favour resorption, or receptor activators of nuclear factor- κ B ligand (RANKL) in fibroblasts, having the same effect (8,15). Likewise, local acidosis induced by infection has been indicated as the cause of the release of bisphosphonates on bone, facilitating osteonecrosis (9). Macrophages and monocytes could intervene in the necrosis mechanism such that by culturing them with solutions of bisphosphonates it has been postulated that these would phagocyte before the macrophages, which would lose their function of responding to the infection (40). All this has led to taking extreme measures against infectious processes to try to reduce the incidence of ONJ in these patients, promoting the application of preventive measures to facilitate the elimination of said sites or their prevention by establishing proper oral healthcare. Placement of a dental implant and surgery associated with this type of treatment is deemed, from the outset, a risk for the emergence of ONJ in susceptible patients, the same as any other surgical procedure, several cases of ONJ having been published after the placement of implants in recent years (16,28). This gave rise to controversy over whether it was appropriate or not to recommend this type of treatment in patients undergoing antiresorptive therapy. Nowadays there is sufficient evidence to affirm that the risk of implant failure caused by osteonecrosis is limited in patients with osteoporosis undergoing treatment with low doses of antiresorptives (1,11,15,18). However, although data is lacking, the risk for patients taking antiresorptives for cancerous lesions -much higher doses-, is considerably more elevated, consequently there is a consensus for stating that implants should be contraindicated in these patients (2,13,14,16). Among the objectives of the protocols described is to inform the patient adequately of the risks that they take if they are wearers or dental implants are placed in relation to the antiresorptive treatment, care-

fully assessing the different risk factors involved, especially in patients with cancer.

In recent years, several cases have been published in which osteonecrosis occurred around implants that had been in place for several months or even years and correctly osseointegrated (13,14,16,28). It would be an implant presence-triggered osteonecrosis, compared to an implant surgery-triggered osteonecrosis. Escobedo *et al.* (17), in a literature review and own series, concluded that peri-implant ONJ occurred more frequently in cases where implants had been loaded at least one year earlier (74 cases compared to 27 cases related to implant insertion). Our protocols take on board this highly significant point, because implant-wearing patients who commence treatment with antiresorptives should be warned that the risk of suffering ONJ will always exist owing to the very presence of the implant, and not just by its placement, therefore one way of preventing it would be not to place implants in any patient who is to be treated or is being treated with these drugs. Similarly, it is essential to prevent any peri-implant infectious process in wearers, the risk being greater in patients with cancer. The increase in risk of ONJ around already osseointegrated implants may be justified by bone remodelling being decreased, such that the peri-implant bone under constant demand from masticatory load could not respond properly to the functional needs and would necrotize. However, ONJ does not always occur, and furthermore different authors have shown an important reduction in the frequency of osteonecrosis in patients who undergo certain preventive measures to avoid infectious sites around their implants, which leads one to think that there must be something else facilitating the emergence of this condition around the implants. Indeed, several publications have suggested that peri-implantitis could be a risk factor for ONJ associated with implants, (9,14,16,28), which reinforces the importance that the infectious/inflammatory theory has been gaining in recent years to explain the etiopathogenesis of ONJ. Thus, Troeltzsch (31) studied a cohort of 316 patients diagnosed with ONJ, of whom 34 were dental implant wearers (117 implants). Of these, 56% (19 patients, 62 implants) developed ONJ around the implants, 56 of which had been placed before commencing antiresorptive treatment, the majority undergoing treatment for cancer, although three patients were being treated for osteoporosis. It should be emphasized that this author found that clinical and radiological signs of peri-implantitis were significantly associated with the emergence of peri-implant ONJ, that is, that said inflammatory process could be involved in the development of their osteonecrosis. The presence of an implant could represent a less resistant site for the development of ONJ, the bone being more vulnerable to infection due to remodelling being decreased, thus, peri-implantitis

induced by bacterial plaque could trigger in this context a condition of osteonecrosis (1,14,15,18). Moreover, emphasis has been placed on the fact that the prejudicial effect of antiresorptives could be aggravated by acidic environments as a result of concomitant infectious processes—for example, peri-implantitis—, which makes the infectious/inflammatory process an important focus for understanding the etiopathogenesis of ONJ (9).

In terms of all the above, and considering the latest knowledge or scientific consensus on the role of bacterial plaque/biofilm in the etiopathogenesis of peri-implant disease, the possibility of preventing ONJ by controlling peri-implant disease would make a lot more sense so that proper control of peri-implant health using appropriate periodontal maintenance protocols could prevent the development of peri-implant mucositis or its transition to peri-implantitis per se, with the risk of it triggering a condition of ONJ in these patients. This is the reason for the inclusion of this type of measures in our protocols.

ONJ treatment using antiresorptives is a real challenge for professionals due to the large number of variables involved, the numerous therapeutic possibilities employed, and the enormous variability of the protocols used in the literature, with very disparate results. Furthermore, many of the treatments used, especially surgical ones' entail in many cases a worsening of the condition with an extension of the lesion. In a study on different therapeutic management approaches in the literature, the authors grouped them into 7 different therapeutic protocols, of which the best results were obtained with conservative treatment, clinical and radiological follow-up, minimally invasive surgical treatment and adjuvant measures (19). This shows the enormous variety of existing proposals and the difficulty in taking decisions when faced with a specific case of osteonecrosis. Furthermore, evidence has shown the efficacy of different preventive measures which have been applied to these patients achieving a decrease in the cases of ONJ, although, likewise on this topic there is enormous variability in studies and different protocols which make it hugely difficult to compare them and bring them together (38).

Different articles report the influence of preventive strategies in the reduction of the incidence of drug related ONJ. Thus, Ripamonti found an incidence of 7.8% of ONJ in patients with lung cancer which fell to 1.7% after the application of preventive measures (25). In patients with multiple myeloma, Dimopoulos obtained an incidence of ONJ of 26.3% in patients with no preventive strategies, which fell to 6.7% in those who did receive said measures (20). Mücke, in patients suffering bone metastases in prostate cancer, obtained an incidence of ONJ of 23.3% in patients who were reviewed once a year by their dentist, which fell to 2.2% in those

for whom meticulous preventive follow-up at 3 months was undertaken (32). Authors such as Bramati (30) or Vandome (29) carried out work along the same lines obtaining similar results. Assessing the above articles overall, preventive measures achieved a reduction in the incidence of ONJ of 77.3%, compared to control groups (37). However, studies supporting this important reduction in the incidence of ONJ with the application of preventive measures, present many methodological discrepancies with each other, such that the type of measures applied and the means of executing them are different, therefore it is complicated to be able to compare the results or decide which of the published protocols is the most suitable one to apply. This is the reason that made us consider trying to bring together all the published evidence, update it and draft global protocols, easy to implement in a dental clinic considering the different possibilities which may be presented with these patients.

It is important to highlight that the quality of evidence for most of the articles which apply preventive measures and which have been described in this study is poor, either because of the small sample size, the short follow-up times, the type of retrospective control used, the application of unclear follow-up protocols, etc., such that we coincide with the authors themselves when they point to the advisability of carrying out controlled randomized prospective studies with larger samples and longer follow-up times to be able to achieve high levels of evidence.

Several studies have shown the efficacy of antibiotic prophylaxis in those patients undergoing treatment with antiresorptives who need some oral surgery procedure. Normally these studies have been conducted in patients who have undergone dental extractions, achieving favourable results because no case of ONJ developed after the application of these protocols. Currently it is a widely accepted measure by the authors, not just for extractions but also when facing any oral surgery that these patients require. (2,25-27,32,33,36). For this reason, this measure has been included in our protocols for any oral surgery procedure, including extractions in these patients, depending on the different circumstances that may be presented arising from the type of treatment they received and the treatment stage at which they find themselves.

The application of these protocols requires an interdisciplinary team which can handle the various treatments and apply the measures contained in them. Thus, it will be necessary to have qualified hygienists who have an in-depth knowledge of the disease in order to provide proper reports to the patients and answer their queries. Similarly, they should have persuasive qualities and motivation to be able to make the patient aware of the importance of looking after their oral health and

maintaining it in an optimal state. Likewise, generalists should be equally well trained for undertaking conservative treatments in the most non-traumatic way possible and be able to diagnose each lesion adequately in order to apply the most suitable treatment that manages to avoid unnecessary extractions in the future. The team of surgeons will also have to be prepared to perform surgery with the same minimal trauma and with suitable antibiotic prophylaxis. It is equally important to maintain contact with the medical team involved in the treatment of the underlying pathology, especially rheumatologists, oncologists, internists and gynaecologists. All the above requires a great staff learning and organization effort, continuous training and coordination of the whole team involved in the preventive management of these patients.

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Conflict of interest

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Authors contributions

M.M.R.R., A.S.G. and M.R.S. have carried out the data collection, the writing of the first draft of the article and has participated in the interpretation of the results. M.M.R.R., M.A.S.F. and D.T.L. have participated in the design of the study, its performance and the interpretation of the results. J.L.G.P., M.M.R.R., D.T.L. and M.A.S.F. have participated in the supervision of the study, in the analysis of the data, in the interpretation of the results and in the writing of the first drafts of the article. All authors have participated in the writing of the final manuscript.