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(See Annex 1)

Osteonecrosis of the Jaw: Consensus document

*Consensus document of the **Spanish Society for Bone and Mineral Metabolism Research (SEIOMM)** in conjunction with: Spanish Association for the Study of the Menopause (AEEM), Hispanic Foundation for Osteoporosis and Metabolic Diseases (FHOEMO), Spanish Society of Mouth Surgery (SECIB), Spanish Society of Oral and Maxillofacial Surgery (SECOM), Spanish Society of Orthopedic Surgery and Traumatology (SECOT), Spanish Society of Endochrinology and Nutrition /SEEN), Spanish Society of Osteoporotic Fractures (SEFRAOS), Spanish Society of Geriatrics and Gerontology (SEGG), Spanish Society for Family and Community Medicine (SEMFyC), Spanish Society of Internal Medicine (SEMI), Spanish Society of Oral Medicine (SEMO), Spanish Society of Doctors in Primary Medicine (SEMERGEN), Spanish Society for Rehabilitation and Physical Medicine (SERMEF), Spanish Society of Rheumatology (SER), Ibero-American Society for Bone and Mineral Metabolism Research (SIBOMM).*

Summary

Our objective has been to write a position statement on the risk of developing maxillary osteonecrosis (ONJ) in patients receiving bisphosphonates for the treatment of osteoporosis, and identifying and evaluating the extent of the evidence which supports the recommendations. In order to do this we have reviewed the published studies on the definition, epidemiology, physiopathology, clinical manifestation, diagnosis and treatment of ONJ, producing, after their analysis, the current recommendations. These have been developed after a pre-agreed and reproducible process, which included an accepted model for the evaluation and citing of the evidence which supports them. The document, once produced by the co-ordinators, was reviewed and discussed by all the members of the panel, who produced draft recommendations which were finally studied and approved by the experts of the medical societies concerned with bone mineral metabolism, listed in Annex 2.

1. Introduction

Osteonecrosis is an infrequent clinical condition, associated with a change in blood supply or an inhibition in osteoblastogenesis and an increase in apoptosis of the osteocytes. In the past osteonecrosis has been associated with diseases such as lupus, falciform cellular anaemia (sickle cell anaemia) or Caisson's disease, or with certain treatments such as the use of corticoids or radiotherapy[1].

In 2003 and 2004 the first cases in patients who took bisphosphonates, of a process which was then named maxillary osteonecrosis (ONJ), were published[2,3]. Bisphosphonates are a group of drugs which are widely used in a large number of metabolic bone diseases, some of which are very frequent in the population of older people, such as osteoporosis. The initial cases of ONJ described were seen in patients who received very high doses of bisphosphonates, in the context of neoplasic disease with metastasis, there being very few cases described among patients receiving these drugs at doses used for osteoporosis. Even so, they generated alarm as much in the scientific community as in the general public. ONJ has a multifactorial etiopathogeny and has also been seen in patients who are not taking bisphosphonates. We have produced this position statement with the intention of clarifying the most controversial aspects of this matter.

2. Definition

The first problem which we encounter when we study ONJ is the absence of a clear and universally accepted definition of the disease. A panel of experts of the American Society for Bone and Mineral Research (ASBMR)[4] recently recommended using the definition of "an area of exposed bone which persists for more than 8 weeks in the absence of previous irradiation and/or metastasis in the jaw". The American Academy of Oral and Maxillofacial Surgeons (AAOMS) has published a very similar definition: patients may have ONJ if they have three requisites: 1) current or previous use of bisphosphonates; 2) presence of exposed or necrotic bone in the maxillofacial region which has persisted for 8 weeks; and 3) absence of maxillatory radiotherapy[5]. In Spain a panel of experts recommends the use of the following criteria for the definition of ONJ in neoplasic patients treated with intravenous bisphosphonates[6]:

1. The patient has received or is receiving treatment with intravenous bisphosphonate.
2. Presence of one or more ulcerous lesions in the mucous membrane of the alveolar processes, with exposure of the maxillary or mandibular bone. There may also be cases without bone exposure, with pain or fistulas, which should be considered as candidates for carrying out a more detailed study.
3. The exposed bone has a necrotic appearance.
4. The lesion occurs spontaneously or, more frequently, following dento-alveolar surgery (especially extractions).
5. Absence of scarring for a period of at least 6 weeks.

The development of these criteria is very important because it allows us to resolve one of the principal problems of ONJ: its identification and diagnosis.

3. Etiopathology

The etiopathology of ONJ is unknown. Nevertheless, a series of factors related to this disease has been described, as follows:

3.a. Changes to the immune system and in repair mechanisms due to neoplasia.
3.b. Vascular disorder
3.c. Low bone regeneration
3.d. Bone toxicity of bisphosphonates
3.e. Toxicity of bisphosphonates in soft tissues
3.f. Other

3.a. Changes to the immune system and repair mechanisms due to neoplasia

Neoplasia exists as an underlying disease in over 95% of patients with ONJ[7]. When metastasis is present neoplasia in itself increases the risk of infection and is associated with a change in the healing of the tissues[8]. On the other hand, patients with neoplasia normally receive medication which has an inhibitive effect on their immune system, such as immunosuppressors or corticoids; and all these, taken together, predispose cancer patients to the development of oral osteomyelitis or to suffering infections in places where dental extractions have been made. In fact, there is, in ONJ, an important infectious component, above all actinomyces[9]. However, it should be noted that all these factors have been present during the past decades, and, therefore, while they may contribute, they do not themselves explain the emergence of ONJ in the last few years.

3.b. Vascular disorder

Given that the disease has been named ONJ, it is stipulated that vascular disorder one of the keys in its etiopathogeny. While we don't know the etiology of ONJ, we do know that the reduction in the vascularization that may exist to a greater or lesser extent is not the only etiopathogenic factor. Thus, Hansen[9] has informed us that the vascular pattern in 7 out of 8 biopsies of patients with ONJ is normal, a finding similar to those described by other authors[10]. For some reason, which escapes us, there has been a tendency to equate ONJ with avascular bone necrosis in other locations, such as the hip, when there is no clinical or physiopathological parallel between the two conditions[7,11,12]. Since in patients with ONJ there is a change in the mucus membrane, the majority showing exposed bone, the possible effect of bisphosphonates on cell proliferation has been investigated. There is some evidence that high doses of bisphosphonates, for example zoledronate, inhibits such proliferation[13], but it is improbable that this effect might in itself be the principle etiological agent of ONJ.

3.c. Low bone remodelling

It has been suggested that a low bone remodeling could be an etiopathegenic factor which could contribute to the development of ONJ. Because of this the hypothesis is postulated that bisphosphonates, which act to inhibit bone reabsorption, used in a high dose in neoplasic patients (precisely those in which ONJ has most frequently been described) encourage the development of maxillary disease; however, it is difficult to confirm a hypothesis in which a reduction in bone regeneration may lead to a change in the healing of the soft tissues following a dental treatment.

In bone histopathological studies of patients with ONJ "frozen-bone" has not been observed. Various authors have described the existence of active reabsorption in over half of patients with ONJ[9,10]. Looking for similarities with other bone diseases, in primary hypoparathyroidism (in which there is low bone remodeling) no cases of ONJ have been described, however, in osteopetrosis there have been some accounts published of cases of osteomyelitis and osteonecrosis[14]. In these cases these lesions have been attributed to the obliteration of the bone medulla by sclerotic bone[15,16].

ONJ has been described only since bisphosphonates have been commercialised and used in daily clinical practice. During the development of clinical trials no cases of this disease were described. Only recently, with zoledronic acid, in the HORIZON study[17-19], was it confirmed that there was no increased risk of ONJ, since, in the end the study found 2 cases, one of which received the drug, and the other, the placebo. Finally, if the lesion is due to an inhibition of bone reabsorption, one needs to take into account the fact that new drugs for the treatment of osteoporosis, such as denosumab or catepsin K inhibitors, which also reduce to a significant extent bone regeneration, are being studied and in which, at least until now, no cases of ONJ have been found.

3.d. Bone toxicity of bisphosphonates

The bisphosphonates are drugs whose action on bone remodelling is to inhibit the activity of the osteoclasts. For this reason it had been thought that ONJ might constitute a manifestation in the bone of this suppression of bone remodelling, especially when high doses are used. Histological studies made in patients with ONJ have shown the existence of empty osteocytic lacunae[9], necrotic osteocytes[10], as well as lacunae containing healthy osteocytes. There are also studies which indicate that bisphosphonates reduce apoptosis in the osteocytes[20].

Since ONJ has been observed above all with the strongest bisphosphonates, administered intravenously[21] and at high doses, combined with the histological findings, has allowed the development of the hypothesis of direct toxicity of bisphosphonates on the bone. However, in contradiction to this is the fact that they affect only the maxillary, and not other, bones, on which the bisphosphonates act equally. On the other hand, no diminution in ability to repair fractures, either in patients affected by ONJ or in different tests carried out with bisphosphonates, have been described[18,22-25], while a recent cohort study showed a significant association between the use of bisphosphonates and pseudoarthritis in fracture of the humerus even though its incidence in absolute terms is minimal[92]. Another study, Abrahamsen et al[93], found that more than 6 years of treatment with alendronate did not increase the risk of femoral fracture.

3.e. Toxicity of bisphosphonates in the soft tissues

Another theory which has recently been published is that the bisphosphonates accumulate in the alveolar bone, both in the jaw as well as in the maxillary bone, producing toxicity in the surrounding soft tissues[32]. The bisphosphonates don't only act on the bone (although it is on bone tissue that they fundamentally act), but also on other cells. On the one hand, the reaction of the acute phase which usually occurs following the intravenous administration of bisphosphonates produces an inhibition of the farnesyl-pyrophosphate-synthase (FPPS) enzyme, which, in the monocytes, induces the activation of the Tγ,δ cells[26]. Similar effects have been described in other cells such as microphages, endothelial cells, tumour cells and osteoblasts[27]. These effects are related to the strength of the bisphosphonates and the amount of time that the cells are exposed to these drugs, which suggests a gradual accumulation in these cells of these drugs over time[7,11,12]. Another study has shown that the proliferation of existing osteoblasts in the periodontal ligament is reduced as the concentration of alendronate in a cultivated medium is increased[28]. In macrophages and other cells, the bisphosphonates penetrate through a process of endocytosis[29] which is unidirectional, and because there is no mechanism of eliminating the drug, will lead to its accumulation.

Finally, what should also be taken into account is that the possibility of gastrointestinal inflammation, oesophagitis and ulcers has been very well documented, observed most often when the bisphosphonates are administered daily by mouth. This secondary effect probably represents a toxicity by contact similar to the oral ulcerations observed when bisphosphonate pills are sucked[30].

3.f. Other

On the other hand, Kamaishi, et al[31] published in 2007 a series of 31 cases of which 18 (58%) were diabetics or those who had altered levels of glucose when fasting, while in the control group, consisting of cancer patients treated with bisphosphonates and without ONJ, the prevalence of diabetes was 12%, and the general population, 16%. In these patients, in two cases (6.4%) neoplasia was not present as an underlying disease (one had osteoporosis and one had rheumatoid arthritis). The authors conclude that diabetes can be a risk factor for ONJ and suggest possible physiopathological mechanisms by which diabetes can increase the effect of the bisphosphonates.

These etiopathogenic factors are not mutually exclusive. In fact is it possible that ONJ might be a disease whose etiopathogeny is multifactorial[7,11,12,32]. On the other hand, it should be noted that in up to 70% of cases the patients had undergone a dental intervention: extractions, implants, etc.[2,3,7,10-12,21,32-34], although in 30% ONJ is observed without such an intervention.

4. Epidemiology

Here we set out information regarding the epidemiology of ONJ, which we have been able to obtain in various ways: a) description and review of cases; b) studies of prevalence based on population; and c) data obtained from pivotal studies.

4.a. Description and review of cases

The first publication of cases of ONJ was produced in 2003 by Marx et al[2]. These authors collected a total of 36 cases of ONJ. All these cases were receiving intravenous bisphosphonate –pamidronate and/or zoledronate– in high doses. In all these cases neoplasia was present as the underlying condition, with the exception of one case of osteoporosis (2.7%). Since it was only a letter to the editor neither the dose or the period of time that the bisphosphonate was given to the patient affected by osteoporosis was specified. One year later, in 2004, Ruggiero et al[3] gathered a total of 63 cases of ONJ, which to date constitutes one of the most important groups of patients. Of these 63 cases, the underlying disease was osteoporosis in 7 patients (11.1%), the rest being cancer patients.

Since then a large number of articles have been published, the majority containing descriptions of isolated cases or series of cases, more or less short[35,36-66]. In these publications the risk factors most frequently found are the presence of underlying neoplasia, which is present in 95% of cases, and the intravenous administration of bisphosphonates[67,68]. Zoledronate is a 3rd generation bisphosphonate which is administered intravenously, and is at present the most potent bisphosphonate available[69]. Thus most of the cases of ONJ are associated with this drug, above all after its commercialisation and almost systematic use in patients affected by neoplasia in whom, clinically, there is a high risk of hypercalcemia and/or bone metastasis, such as occurs in multiple myeloma, prostate cancer, breast cancer and lymphatic cancer[4].

The working group on ONJ of the American Society for Bone and Mineral Research (ASBMR) carried out a review of cases of ONJ published in PubMed and Medline and found a total of 57 cases of ONJ in patients treated with bisphosphonates for osteoporosis and 7 cases in patients affected by Paget's disease. Of the 57 cases of osteoporosis, most had received alendronate, two risedronate, one a combination of alendronate and risedronate, and two pamindronate and/or zoledronate intravenously. The conclusion of the working group was that the risk of ONJ associated with therapy with bisphosphonates for osteoporosis was between 1/10,000 and 1/100,000 patients/treatment years[70].

4.b. Prevalence studies based on population

Two broad studies have been published of patients receiving bisphosphonates and both have confirmed that the risk of ONJ in patients who do not have cancer is very low:

- A study carried out in Germany, which included 780,000 patients who received bisphosphonates for osteoporosis, found three cases of ONJ, with a prevalence estimated at 0.00038%, which equates to the risk of one case for each 100,000 patients per year[71]. This study has the limitation that the diagnosis of ONJ could not be verified.

- On the other hand, Australian researchers carried out a postal survey looking for cases of ONJ related to bisphosphonates. They obtained 154 cases of which 114 had neoplasia, 8 Paget's disease and 36 osteoporosis. All the patients in the osteoporosis group had received alendronate. They estimated a frequency of ONJ of between 0.04% and 0.01%, increasing to between 0.09% and 0.34% in patients having had an extraction. The study had many methodological limitations, such as, for example, the fact that the information used was gathered using the post without the ability to confirm, or not, the existence of ONJ, and without the ability, also, of excluding the possibility of duplicate cases; in addition, they only collected cases from the public medicine system and none from the private medicine system[22-24,72-74].

4.c. Randomised clinical trials

Given that ONJ was a disease which did not used to be associated with the drugs when the pivotal studies were carried out with the different bisphosphonates, information which could have been produced in these studies is not available with either etidronate, alendronate, risedronate or ibandronate[18]. Neither were the trials designed to record adverse secondary effects in the oral cavity.

On the contrary, in the HORIZON study, which is pivotal for zoledronic acid, possible cases of ONJ were recorded. This study, carried out on 7,736 women, administered 5 mg of zoledronate to the treated group and a placebo to the control group, supplemented by calcium and vitamin D in both groups. At the end of the study two cases of ONJ were found, one in each group, from which it was concluded that zoledronic acid at the dose used for the treatment of osteoporosis (5mg intravenous, annually) does not increase the risk of ONJ[5,17].

5. Clinical stages of ONJ

The AAOMS has described the following clinical stages in ONJ[75]:

Stage I The presence of exposed or necrotic bone in asymptomatic patients, with no evident signs of infection.

Stage II The presence of exposed or necrotic bone in patients, with pain and evident signs of infection.

Stage III The presence of exposed or necrotic bone with pain, infection and one or more of the following signs: pathological fracture, extra-oral fistula or osteolysis extending to the lower edge.

6. Diagnosis

The first problem we have at present in diagnosing ONJ is the absence of a universally accepted, single definition of the disease. For this reason we must opt for that which adapts best to our clinical circumstances.

The panel of experts of the ASBMR recommends differentiating between a **confirmed case**, which is defined as an area of exposed bone in the maxillofacial region which is not cured after 8 weeks after its identification by a specialist, in a patient being treated with bisphosphonates and who has not received craniofacial radiotherapy treatment. 8 weeks is the period of time in which most traumas, extractions and surgical procedures which could damage the soft tissues, are healed. In cases in which the lesion might have appeared spontaneously, or in which the period over which it has developed is not known, the period of 8 weeks starts from the moment at which the specialist (doctor, odontologist) had documented the lesion. A **suspected case** would be when the same circumstances as above have occurred but in which the 8 weeks have not passed. These suspected cases should be kept under observation until the confirmation, or not, of the existence of ONJ[76].

6.a. Biochemical markers for bone remodelling and ONJ

In a study published by Marx et al[76], the authors found that the biochemical marker for bone remodelling was "telopeptide C-terminal of collagen type I" in the blood (CTX) when fasting, and observed that there was a correlation between its levels and the length of period of use of oral bisphosphonates, suggesting that an increase in values of CTX in the blood could indicate a recuperation of bone remodelling, which happens when the treatment with bisphosphonates is suspended. In addition, they stratified the relative risk of suffering ONJ in such a way that values of CTX lower than 100pg/ml would represent a high risk, values of between 100pg/ml and 150pg/ml indicate a medium risk and values over 150pg/ml, a low risk. Levels of CTX in the blood increase by between 25.9 and 26.4pg/ml for each month of a break in therapy indicating, according to the authors, a recuperation of bone remodelling. High values of CTX in the blood – above 150pg/ml - could be used as a guide for oral surgery procedures since the authors observe healing of mouth lesions either spontaneously or after receiving the appropriate treatment, or, on the other hand delaying mouth surgery in those patients who have levels of CTX in the blood lower than 150 pg/ml. This study has since been criticised by other authors who do not agree with the recommendations made by Marx et al[4,77,78]. This includes the ASBMR working group which having recently published a position paper on ONJ[79], published an *addendum* in which they clarified that CTX blood level values could not be taken as a "golden rule" which enables the prediction of the development, or not, of ONJ following dental surgery[80].

7. Already-established treatment of ONJ

The already-established medical and surgical treatment of ONJ can be found in numerous guides to clinical practice, both national[6,81-83] and international[4,75,84-86], to which the interested reader are referred, since it is moving away from the objectives of this document.

8. ONJ as a complication in the treatment of osteoporosis

Most cases of ONJ are observed in patients who have underlying neoplasia, those most frequent described being multiple myeloma, breast cancer, prostate cancer, and others[4].

The few studies that are available have confirmed that the risk of ONJ in patients receiving bisphosphonates for osteoporosis is very low, in the order of 1 case per 100,000 prescriptions of bisphosphonate. So, the ASBMR working group estimates that the risk of ONJ associated with therapeutic use of bisphosphonates for osteoporosis was between 1/10,000 and 1/100,000 patient/treatment years[87]. As mentioned in the previous section, in the work published in Germany, they found a risk of 1 case in every 100,000 patient years[71] and in Australia it was between 1 and 4 cases for every 10,000 patients[17-19].

On the other hand, the HORIZON study, the only study which has documented the appearance of ONJ as an adverse effect, did not find an increase in the risk of ONJ in patients receiving bisphosphonates, in this instance intravenously[86].

9. Position statements and clinical guides from medical, surgical and odontological societies concerning ONJ

The expert authors of position statements and clinical guides have agreed in general, on two facts: on the one hand they recognise the scarceness of scientific evidence, and the need, therefore, to make recommendations based on the opinions of experts; and on the other hand, there have recently been published, in a short period of time, updates which are largely converging in the view that the risk of ONJ from bisphosphonates utilized at doses used for the treatment of osteoporosis is very low, when previously they had issued warnings on this matter.

The American Association of Oral Medicine published in 2005 a position statement which indicated that patients who were at risk of developing ONJ were those suffering from multiple myeloma or metastatic cancer patients in whom intravenous bisphosphonates were used, but also in patients receiving bisphosphonates for osteoporosis. They recognised the lack of clinical guides based on evidence and that those that did exist were based on the opinion of experts[84].

Recently, in December 2008, the American Dental Association (ADA) published an updated version of their recommendations for the management of patients receiving bisphosphonates by mouth. This document updates the recommendations made by this association in 2006. Following a detailed review of available literature, the ADA indicates that the risk of developing ONJ apparently remains low. In addition, they say that we do not have the direct evidence to identify patients at high risk of developing this complication. In another document also published by the ADA, specifically on the dental management of those patients who are receiving bisphosphonates, the authors conclude that there is not a single piece of evidence of any kind and, therefore, state that stomatologists and odontologist should act "following their own criteria"[88].

The Canadian Association of Oral and Maxillofacial Surgeons (CAOMS) published a position statement in 2008[89]. This document pays much attention to the previous state of oral hygiene of the patient. In patients with adequate oral health the authors state that there is absolutely no problem with initiating treatment with bisphosphonates, be it oral or intravenous, providing that there is a six-monthly check up[89]. If preventative mouth care has not been carried out or if there is a dental emergency, these problems should be resolve before the start of treatment with bisphosphonates. If patients are already receiving bisphosphonates and present with a real dental emergency, invasive surgery should not be delayed, although consideration should be given to suspending the bisphosphonate treatment during the period of healing. For patients who require non-emergency invasive dental treatment, the bisphosphonate treatment should be interrupted for some months before the intervention until the wound is healed. However, we did not find any clinical studies which concerned themselves with the convenience, or not, or with the duration, of this interruption of treatment.

In Spain some consensus documents have been published, sponsored by Professor Bagan[6,81], and others by different societies such as the Spanish Society for Oral and Maxillofacial Surgery[83]. The first, from 2006[82], centred on patients with neoplasia and having intravenous bisphosphonates, brings together recommendations as much for the prevention as specifically for the treatment of already established ONJ, even proposing a form for gathering data in a uniform way. In this first document it is recommended that, when a patient receives intravenous bisphosphonate at doses used for neoplasia, they should be monitored by the odontologist/stomatologist at least once a year, to detect, and in which case, treat, caries and periodontal disease at an early stage.

In an later work Balgan, et al[6] promoted a protocol for those patients who are going to start treatment with intravenous zoledronic acid for their neoplasic pathology, which were previously evaluated and treated by an oral hygiene professional.

ANNEX 1

Co-ordinator

Manuel Sosa Henríquez

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- Manuel Sosa Henríquez, President SEIOMM
- María Jesús Gómez de Tejada Romero, Secretary SEIOMM
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ANNEX 2

Co-ordinator
Spanish Foundation for Bone and Mineral Metabolism Research (FEIOMM)
Spanish Society for Bone and Mineral Metabolism Research (SEIOMM)

Scientific Societies
Societies which participated in this position statement:
- Spanish Association for the Study of the Menopause (AEEM)
Reviewer and President: Javier Ferrer Barriendos
- Hispanic Foundation for Osteoporosis and Metabolic Diseases (FHOEMO)
Reviewer and President: Manuel Díaz Curiel
- Spanish Society of Mouth Surgery (SECIB)
Reviewer and President: José Mª Martínez-González
- Spanish Society of Oral and Maxillofacial Surgery (SECOM)
Reviewer and President: Rafael Martín-Granizo López
- Spanish Society of Orthopedic Surgery and Traumatology (SECOT)
Reviewer: Fernando Marco Martínez, President: Enric Cáceres Palou
- Spanish Society of Endochrinology and Nutrition (SEEN)
Reviewer: Manuel Muñoz Torres, President: Tomas Lucas Morante
- Spanish Society of Osterporotic Fractures (SEFRAOS)
Reviewer: Adolfo Díez Pérez, President: Antonio Herrera Rodríguez
- Spanish Society of Geriatrics and Gerontology (SEGG)
Reviewer: Carmen Navarro Ceballos, President: Pedro Gil Gregorio
- Spanish Society for Family and Community Medicine (SEMFyC)
Reviewers: José SanFélix Genovés / Vicente Giner Ruiz, President: Luis Aguilera García
- Spanish Society of Internal Medicine (SEMI)
Reviewer: José Antonio Blázquez Cabrera, President: Pedro Conthe Gutiérrez
- Spanish Society of Oral Medicine (SEMO)
Reviewer and President: Antonio Bascones Martínez
- Spanish Society for Doctors in Primary Medicine (SEMERGEN)
Reviewer: Carmen Valdés Llorca, President: Julio Zarco Rodríguez
- Spanish Society for Rehabilitation and Physical Medicine (SERMEF)
Reviewers: Elena Martínez Rodríguez / Andrés Peña Arrébola, President: Inmaculada García Montes
- Spanish Society for Rheumatology (SER)
Reviewer: Javier del Pino Montes, President: Rosario García de Vicuña
- Ibero-American Society for Bone and Mineral Metabolsim Research (SIBOMM)
Reviewer and President: Daniel Salica

Position statement of the Spanish Society for Bone and Mineral Metabolism Research (SEIOMM), and societies related to bone mineral metabolism, on osteonecrosis of the jaws and bisphosphonates used in the treatment of osteporosis

Materials and Methods

The methodology which has been followed has been that of the consensus of the panel of experts. The document generated has been sent to the scientific societies listed in Annex 2. The suggestions or amendments made have been raised with the panel of experts, who have accepted or rejected them, before being re-presented for their reappraisal by the participating societies. The final document brings together the results of this whole process.

Questions produced by the panel of experts

The panel of experts, who met to review the first part of this document, raised the following questions:

1. What is the risk of a patient who is being treated with bisphosphonates for their osteoporosis suffering ONJ?

2. Is there a profile of a patient being treated with bisphosphonates for their osteoporosis, which could be at higher risk of developing ONJ if they were going to undergo a dental operation?

3. Should bisphosphonate treatment be suspended before any such dental operation?

4. Is there any complementary test which allows the establishment - unequivocally, or with a high margin of safety – the risk of suffering ONJ?

Recommendations of the panel of experts on the risk of ONJ in patients receiving bisphosphonates for the treatment of osteoporosis

1. It is estimated that the risk of developing ONJ in the context of treatment of osteoporosis is in the region of 1 case for each 100,000 patient/years.

2. Although the risk of ONJ in patients treated for osteoporosis is very low, a series of factors associated with a higher risk of ONJ have been described (Table 1). The predictive ability of each

of these factors is not established and is extremely low in terms of absolute risk.

The panel considers that, among patients treated with bisphosphonates at the doses used for osteoporosis, those with a previous history of ONJ, those being treated with immunosuppressors and those undergoing prolonged treatment with bisphosphonates have a higher risk of developing ONJ.

3. Conservative odontological treatment can be carried out at any time without previous suppression of treatment with bisphosphonates: on the other hand:

3.a. In patients who are taking bisphosphonates at the dose required for the treatment of osteoporosis for less than 3 years and who don't have additional risk factors, it is not necessary to change or delay surgery if it is required. This includes all odontostomatological surgery. These patients should be attend periodical reviews.

3.b. In cases in which individuals are taking bisphosphonates at the dose required for treatment of osteoporosis for less than 3 years and at the same time are having therapy with corticoids, contact should be made with the prescribing doctor to evaluate the possibility of suspending the bisphosphonate treatment at least 3 months before the oral surgery, except if the risk of fracture in the patient is high (age > 70 years, presence of previous fracture, densitometry with T-score <-2.0), in which case it is not necessary to suspend treatment. In case of suspension, the treatment should be reinstated as soon as healing occurs.

3.c. In patients who are taking bisphosphonates at the dose required for treatment of osteoporosis for more than 3 years, who are those most in need of treatment for this disease, it is necessary to especially evaluate the risk of bone fracture and compare it with the risk of ONJ. The prescribing doctor should be contacted to consider suspension of treatment at least 3 months before surgery, except when the risk of a fracture in the patient is high (age > 70 years, presence of previous fractures, T-score < -3,0) in which case it should not be suspended. In case of suspension, the treatment should be reinstated as soon as healing occurs, see algorithm on page 49.

4. The panel had the view that not a single complementary test has shown the sensitivity or specificity for the prediction and early diagnosis of ONJ. Some authors have recommended the use of blood sCTX as a marker for risk, but at present there is no solid scientific evidence which validates its use. The reasons are[90]:

a) The values proposed as indicating high risk of suffering ONJ are within the range of reference of sCTX in premenopausal women who are healthy and not in treatment, even if there is a significant variation in the ranges of reference according to different studies and analytical methods.

b) For the interpretation of the values of sCTX the co-efficient of variation (CV) needs to be taken into account, which integrates the analytical and biological variabilities. In the case of sCTX this CV is high.

c) The CV determines the minimum significant change or critical difference, which is the minimum change (in %) in the value of the marker between two consecutive demarcations which indicate a real and significant change in the activity of the process. The minimum significant change of sCTX is not well established, varying between 30 and 60% according to different studies.

d) Different commercial kits for sCTX give disparate results. It is necessary to establish standardised laboratory protocols to determine the CV, to calculate the minimum significant change and to establish well defined ranges of reference for sCTX.

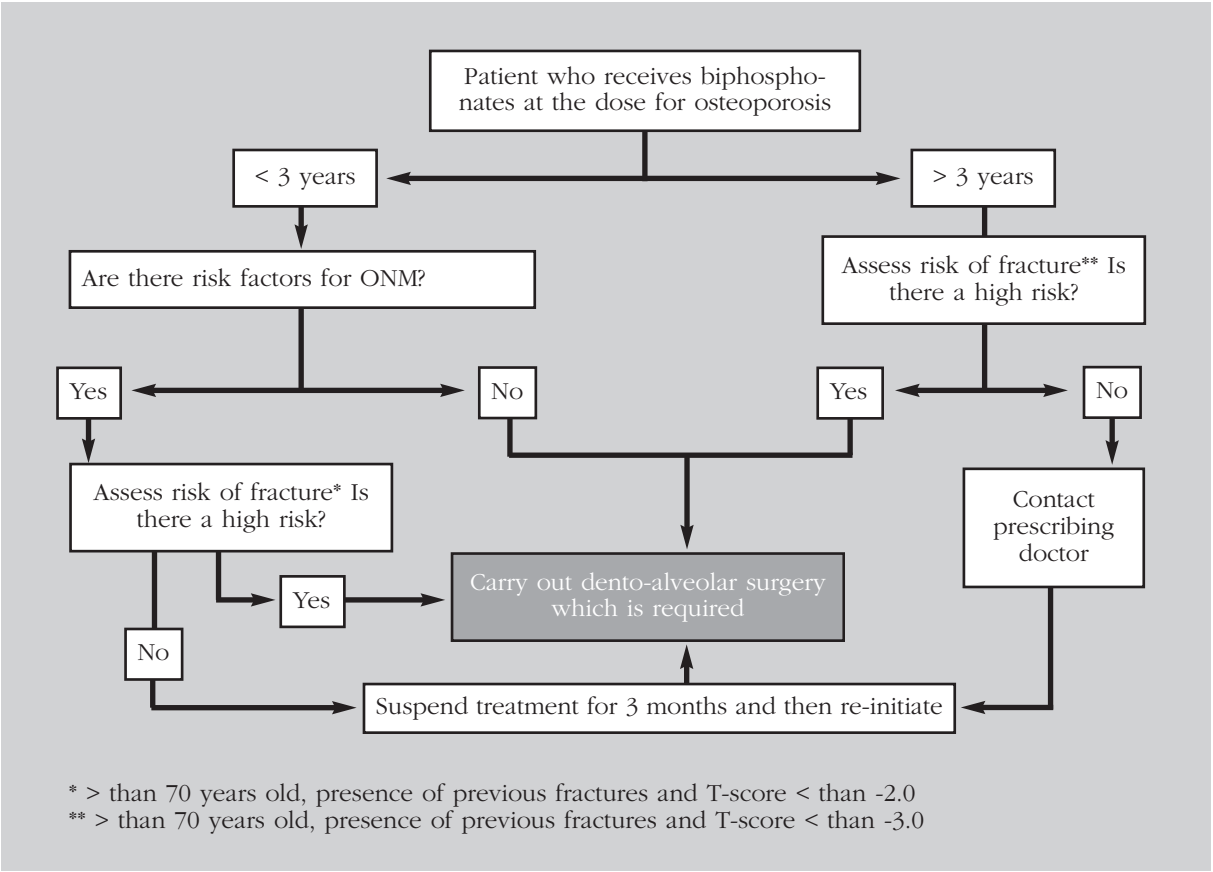
e) There are no controlled studies available which guarantee the use of sCTX as a predictive marker for ONJ. The predictive ability of sCTX for ONJ should be explored through ROC curves to identify sensitivity, specificity, positive predictive value and negative predictive value.

Table 1. List of risk factors described as being associated with ONJ*[91]

-Chemotherapy
-Cancer
-Immunotherapy
-Diabetes mellitus
-Female sex. Oestrogens
-Changes in coagulation
-Infections
-Tobacco
-Dental risk factors: periapical pathology, periodontal disease, dental abscesses, surgical procedures which affect the bone, trauma caused by poorly adjusted dental prostheses
-Drepanocytosis
-Systemic erythematous lupus
-Variations in atmospheric pressure
-Haemodialysis
-Hypersensitivity reactions
-Hypothyroidism
-Storage diseases
-Corticoids
-High blood pressure
-Arthritis
-Blood dyscrasias
-Vascular disease
-Alcohol abuse
-Malnutrition
-Advanced age
-Gaucher's disease
-HIV infection
-Chronic inactivity
-Hyperlipidemia and fat embolism
-Osteoporosis
-Neurological damage

**Factors listed in at least one publication, without there being a clear differentiation between those patients treated with bisphosphonates for neoplasia as for osteoporosis.*

Algorithm



Bibliography

1. Sambrook PN, Ebeling P. Osteonecrosis of the jaw. Curr Rheumatol Rep 2008;10:97-101.
2. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. J Oral Maxillofac Surg 2003;61:1115-7.
3. Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. J Oral Maxillofac Surg 2004;62:527-34.
4. Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D et al. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res 2007;22:1479-91.
5. Compston J. Oral bisphosphonates and osteonecrosis of the jaw: are the MHRA recommendations appropriate? Menopause Int 2007;13:54-5.
6. Bagán JV, Diz-Dios P, Gallego L, Infante-Cossío P, Jiménez Y, Junquera LM et al. Recomendaciones para la prevención de la osteonecrosis de los maxilares (ONM) en pacientes con cáncer tratados con bifosfonatos intravenosos. Med Oral Patol Oral Cir Bucal 2008;13:161-7.
7. Reid I. Pathogenesis of osteonecrosis of the Jaw. IBMS Bonekey 2008;2:69-77.
8. Kudravi SA, Reed MJ. Aging, cancer, and wound healing. In vivo (Athens, Greece) 2000;14:83-92.
9. Hansen T, Kunkel M, Weber A, James Kirkpatrick C. Osteonecrosis of the jaws in patients treated with bisphosphonates - histomorphologic analysis in comparison with infected osteoradionecrosis. J Oral Pathol Med 2006;35:155-60.
10. Bartl R MG. Bisphosphonateassociated osteonecrosis of the jaw: a pathophysiologic approach. Bone 2008;42(Suppl 1):76.
11. Reid IR. Osteonecrosis of the jaw: who gets it, and why? Bone 2009;44:4-10.
12. Reid IR, Cundy T. Osteonecrosis of the jaw. Skeletal Radiol 2009;38:107.
13. Fournier P, Boissier S, Filleur S, Guglielmi J, Cabon F, Colombel M et al. Bisphosphonates inhibit angiogenesis in vitro and testosterone-stimulated vascular regrowth in the ventral prostate in castrated rats. Cancer Res 2002;62:6538-44.
14. Lam DK, Sandor GK, Holmes HI, Carmichael RP, Clokie CM. Marble bone disease: a review of osteopetrosis and its oral health implications for dentists. J Can Dent Assoc 2007;73:839-43.
15. Satomura K, Kon M, Tokuyama R, Tomonari M, Takechi M, Yuasa T et al. Osteopetrosis complicated by osteomyelitis of the mandible: a case report including characterization of the osteopetrotic bone. Int J Oral Maxillofac Surg 2007;36:86-93.
16. Albuquerque MA, Melo ES, Jorge WA, Cavalcanti MG. Osteomyelitis of the mandible associated with autosomal dominant osteopetrosis: a case report. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2006;102:94-8.
17. Colon-Emeric CS, Caminis J, Suh TT, Pieper CF, Janning C, Magaziner J et al. The HORIZON Recurrent Fracture Trial: design of a clinical trial in the prevention of subsequent fractures after low trauma hip fracture repair. Curr Med Res Opin 2004;20:903-10.
18. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA et al. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. The N Engl J Med 2007;356:1809-22.

19. Lyles KW, Colon-Emeric CS, Magaziner JS, Adachi JD, Pieper CF, Mautalen C et al. Zoledronic Acid in Reducing Clinical Fracture and Mortality after Hip Fracture. N Engl J Med 2007;357:1799-809.
20. Plotkin LI, Lezcano V, Thostenson J, Weinstein RS, Manolagas SC, Bellido T. Connexin 43 is required for the anti-apoptotic effect of bisphosphonates on osteocytes and osteoblasts in vivo. J Bone Miner Res 2008;23:1712-21.
21. Cartsos VM, Zavras AI. Bisphosphonate use and the risk of adverse jaw outcomes: a medical claims study of 714,217 people. J Am Dent Assoc 2008;139:23-30.
22. Reginster J, Minne HW, Sorensen OH, Hooper M, Roux C, Brandi ML et al. Randomized trial of the effects of risedronate on vertebral fractures in women with established postmenopausal osteoporosis. Vertebral Efficacy with Risedronate Therapy (VERT) Study Group. Osteoporos Int 2000;11:83-91.
23. Harris ST, Watts NB, Genant HK, McKeever CD, Hangartner T, Keller M et al. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. JAMA 1999;282:1344-52.
24. Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet 1996;348:1535-41.
25. Bone HG, Devogelaer JP, Tucci JR, Emkey RD, Tonino RP, Rodriguez-Portales JA et al. Alendronate Phase III Osteoporosis Treatment Study Group. Ten years' experience with alendronate for osteoporosis in postmenopausal women. N Engl J Med 2004;350:1189-99.
26. Hewitt RE, Lissina A, Green AE, Slay ES, Price DA, Sewell AK. The bisphosphonate acute phase response: rapid and copious production of proinflammatory cytokines by peripheral blood gd T cells in response to aminobisphosphonates is inhibited by statins. Clin Exp Immunol 2005;139:101-11.
27. Roelofs AJ, Gordon S, Rogers MJ. Molecular mechanisms of action of bisphosphonates: current status. Clin Cancer Res 2006;15:6222s-30s.
28. Correia Vde F CC, Caldeira CL, Marques MM. Cytotoxicity evaluation of sodium alendronate on cultured human periodontal ligament fibroblasts. Dent Traumatol 2006;22:312-7.
29. Thompson K, Coxon FP, Crockett JC. Cytosolic entry of bisphosphonate drugs requires acidification of vesicles after fluid-phase endocytosis. Mol Pharmacol 2006;69:1624-32.
30. Rubegni P. Images in clinical medicine. Bisphosphonate-associated contact stomatitis. N Engl J Med 2006;355:e25.
31. Kamaishi M, Yarom N, Avni B, Leitersdorf E, Raz I, Elad S. Possible association between diabetes and bisphosphonate-related jaw osteonecrosis. J Clin Endocrinol Metab 2007;92:1172-75.
32. Reid IR, Grey AB. Is bisphosphonate-associated osteonecrosis of the jaw caused by soft tissue toxicity? Bone 2007;41:318-20.
33. Marx RE, Sawatari Y, Fortin M, Broumand V. Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: risk factors, recognition, prevention, and treatment. J Oral Maxillofac Surg 2005;63:1567-75.
34. Marx RE, Sawatari Y, Fortin M, Broumand V. Risk factors, recognition, prevention, treatment of bisphosphonate- induced osteonecrosis of the jaws. J Oral Maxillofac Surg 2006;64:96.
35. Brooks JK, Gilson AJ, Sindler AJ, Ashman SG, Schwartz KG, Nikitakis NG. Osteonecrosis of the jaws associated with use of risedronate: report of 2 new cases. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 2007;103:780-6.
36. Aragon-Ching JB, Ning YM, Chen CC, Latham L, Guadagnini JP, Gulley JL et al. Higher incidence of Osteonecrosis of the Jaw (ONJ) in patients with metastatic castration resistant prostate cancer treated with anti-angiogenic agents. Cancer Invest 2009;27:221-6.
37. Badros A, Terpos E, Katodritou E, Goloubeva O, Kastritis E, Verrou E et al. Natural history of osteonecrosis of the jaw in patients with multiple myeloma. J Clin Oncol 2008;26:5904-9.
38. Barker K, Lowe D, Olujohungbe A, Low E, Rogers SN. Survey of members of myeloma UK on biphosphontes associated jaw osteonecrosis. Br J Haematol 2007;139:626-8.
39. Borrás-Blasco J, Rosique-Robles D, Giner-Marco V, Galan-Brotons A, Casterá E, Costa S. Possible delayed onset of osteonecrosis of the jaw in association with zoledronic acid. J Clin Pharm Ther 2007;32:651-4.
40. Cetiner S, Sucak GT, Kahraman SA, Aki SZ, Kocakahyaoglu B, Gultekin SE et al. Osteonecrosis of the jaw in patients with multiple myeloma treated with zoledronic acid. J Bone Miner Metab 2009(PMID:19240969).
41. Fehm T, Beck V, Banys M, Lipp HP, Hairass M, Reinert S et al. Bisphosphonate-induced osteonecrosis of the jaw (ONJ): Incidence and risk factors in patients with breast cancer and gynecological malignancies. Gynecol Oncol 2009;112:605-9.
42. García Sáenz JA, López Tarruella S, García Paredes B, Rodríguez Lajusticia L, Villalobos L, Díaz Rubio E. Osteonecrosis of the jaw as an adverse bisphosphonate event: three cases of bone metastatic prostate cancer patients treated with zoledronic acid. Med Oral Patol Oral Cir Bucal 2007;12:E351-6.
43. Ibrahim T, Barbanti F, Giorgio-Marrano G, Mercatali L, Ronconi S, Vicini C et al. Osteonecrosis of the jaw in patients with bone metastases treated with bisphosphonates: a retrospective study. Oncologist 2008;13:330-6.
44. Kyrgidis A, Barbas A. Osteonecrosis of the jaw among bisphosphonate users. Am J Med 2008;121:e21; author reply e3.
45. Mehta RS, Chwistek M. Bisphosphonates and osteonecrosis of the jaw #196. J Palliat Med 2008;11:1039-40.
46. Montazeri AH, Erskine JG, McQuaker IG. Oral sodium clodronate induced osteonecrosis of the jaw in a patient with myeloma. Eur J Haematol 2007;79:69-71.
47. Mouri Y, Yoshida M, Nakano S, Yorozuya K, Fujii K, Fukutomi T et al. A case of osteonecrosis of the jaw in a breast cancer patient with bone metastases receiving long-term treatment with bisphosphonates. Breast Cancer 2009;16:147-50.
48. Naveau A, Naveau B. Osteonecrosis of the jaw in patients taking bisphosphonates. Joint Bone Spine 2006;73:7-9.
49. Ortega C, Montemurro F, Faggiuolo R, Vormola R, Nanni D, Goia F et al. Osteonecrosis of the jaw in prostate cancer patients with bone metastases treated with zoledronate: a retrospective analysis. Acta Oncol (Stockholm, Sweden) 2007;46:664-8.
50. Reilly MM. Osteonecrosis of the jaw in a patient receiving bisphosphonate therapy. Oncol Nurs Forum 2007;34:301-5.
51. Sedghizadeh PP, Stanley K, Caligiuri M, Hofkes S, Lowry B, Shuler CF. Oral bisphosphonate use and the prevalence of osteonecrosis of the jaw: an institutional inquiry. J Am Dent Assoc 2009;140:61-6.
52. Van Poznak C, Estilo C. Osteonecrosis of the jaw in cancer patients receiving IV bisphosphonates. Oncol (Williston Park, NY) 2006;20:1053-62; discussion 65-6.
53. Vannucchi AM, Ficarra G, Antonioli E, Bosi A. Osteonecrosis of the jaw associated with zoledronate therapy in a patient with multiple myeloma. Br J Haematol 2005;128:738.
54. Vieillard MH, Maes JM, Penel G, Facon T, Magro L, Bonneterre J et al. Thirteen cases of jaw osteonecrosis in patients on bisphosphonate therapy. Joint Bone Spine 2008;75:34-40.
55. Vomvas D, Vassiliou V, Papavasileiou D, Kalogeropoulou C, Nicolatou-Galitis O, Kardamakis D. Osteonecrosis of the jaw in a patient treated with ibandronate. J Buon 2008;13:441-2.

56. Walter C, Al-Nawas B, Grotz KA, Thomas C, Thuroff JW, Zinser V et al. Prevalence and risk factors of bisphosphonate-associated osteonecrosis of the jaw in prostate cancer patients with advanced disease treated with zoledronate. Eur Urol 2008;54:1066-72.
57. Zarychanski R, Elphee E, Walton P, Johnston J. Osteonecrosis of the jaw associated with pamidronate therapy. Am J Hematol 2006;81:73-5.
58. Zervas K, Verrou E, Teleioudis Z, Vahtsevanos K, Banti A, Mihou D et al. Incidence, risk factors and management of osteonecrosis of the jaw in patients with multiple myeloma: a single-centre experience in 303 patients. Br J Haematol 2006;134:620-3.
59. Freiberger JJ, Padilla-Burgos R, Chhoeu AH, Kraft KH, Boneta O, Moon RE et al. Hyperbaric oxygen treatment and bisphosphonate-induced osteonecrosis of the jaw: a case series. J Oral Maxillofac Surg 2007;65:1321-7.
60. Junquera L, Gallego L, Villarreal P. Radiology quiz case. Osteonecrosis of the jaw: aminobisphosphonate epidemic. Arch Otolaryngol Head Neck Surg 2008;134:1229-31.
61. Kubo N, Katayama K, Ishizaki A, Morinaga N, Negishi T, Kuwano H. A case of osteonecrosis of the lower jaw due to bisphosphonates in a breast cancer patient with bone metastasis. Gan to Kagaku Ryoho 2008;35:1973-5.
62. Landesberg R, Wilson T, Grbic JT. Bisphosphonate-associated osteonecrosis of the jaw: conclusions based on an analysis of case series. Dent Today 2006;25:52,4-7.
63. Langer CJ. Osteonecrosis of the jaw, a recently recognized sequela of bisphosphonate therapy: case report. Support Cancer Ther 2006;3:122-4.
64. Reiriz AB, De Zorzi Pde M, Lovat CP. Bisphosphonates and osteonecrosis of the jaw: a case report. Clin (Sao Paulo, Brazil) 2008;63:281-4.
65. Saussez S, Javadian R, Hupin C, Magremanne M, Chantrain G, Loeb I et al. Bisphosphonate-related osteonecrosis of the jaw and its associated risk factors: a Belgian case series. Laryngoscope 2009;119:323-9.
66. Wessel JH, Dodson TB, Zavras AI. Zoledronate, smoking, and obesity are strong risk factors for osteonecrosis of the jaw: a case-control study. J Oral Maxillofac Surg 2008;66:625-31.
67. Djulbegovic B, Wheatley K, Ross J, Clark O, Bos G, Goldschmidt H et al. Bisphosphonates in multiple myeloma. Cochrane Database Syst Rev (Online) 2002(3):CD003188.
68. Lipton A, Cook RJ, Major P, Smith MR, Coleman RE. Zoledronic acid and survival in breast cancer patients with bone metastases and elevated markers of osteoclast activity. Oncol 2007;12:1035-43.
69. Brown JE, Ellis SP, Lester JE, Gutcher S, Khanna T, Purohit OP et al. Prolonged efficacy of a single dose of the bisphosphonate zoledronic acid. Clin Cancer Res 2007;13:5406-10.
70. Felsenberg D. Osteonecrosis of the jaw--a potential adverse effect of bisphosphonate treatment. Nat Clin Pract 2006;2:662-3.
71. Sambrook P, Olver I, Goss A. Bisphosphonates and osteonecrosis of the jaw. Aust Fam Physician 2006;35:801-3.
72. Storm T, Thamsborg G, Steiniche T, Genant HK, Sorensen OH. Effect of intermittent cyclical etidronate therapy on bone mass and fracture rate in women with postmenopausal osteoporosis. N Engl J Med 1990;322:1265-71.
73. McClung MR, Geusens P, Miller PD, Zippel H, Bensen WG, Roux C et al. Effect of risedronate on the risk of hip fracture in elderly women. Hip Intervention Program Study Group. N Engl J Med 2001;344:333-40.
74. Chesnut IC, Skag A, Christiansen C, Recker R, Stakkestad JA, Hoiseth A et al. Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. J Bone Miner Res 2004;19:1241-9.
75. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. J Oral Maxillofac Surg 2007;65:369-76.
76. Marx RE, Cillo JE Jr, Ulloa JJ. Oral bisphosphonate-induced osteonecrosis: risk factors, prediction of risk using serum CTX testing, prevention, and treatment. J Oral Maxillofac Surg 2007;65:2397-410.
77. Assael L. Serum CTX to prevent osteonecrosis/orthodontic extraction of third molars: paths toward minimizing surgical risk? J Oral Maxillofac Surg 2007;65:2395-6.
78. Schwartz HC. Serum CTX testing. J Oral Maxillofac Surg 2008;66:1319-20; author reply 20.
79. Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D et al. Oral bisphosphonate-induced osteonecrosis: risk factors, prediction of risk using serum CTX testing, prevention, and treatment. J Oral Maxillofac Surg 2008;66:1320-1; author reply 1-2.
80. Woo SB, Hellstein JW, Kalmar JR. Systematic review: bisphosphonates and osteonecrosis of the jaws. Ann Int Med 2006;144:753-61.
81. Bagan J, Blade J, Cozar JM, Constela M, García Sanz R, Gómez Veiga F et al. Recommendations for the prevention, diagnosis, and treatment of osteonecrosis of the jaw (ONJ) in cancer patients treated with bisphosphonates. Med Oral Patol Oral Cir Bucal 2007;12:E336-40.
82. Bagán JV, Blade J, Cozar JM, Constela M, García Sanz R, Gómez Veiga F et al. Recomendaciones para la prevención, diagnóstico y tratamiento de osteonecrosis de los maxilares (ONM) en pacientes con cáncer tratados con bifosfonatos. Med Oral, Patol Oral, Cir Bucal 2007;12:279-283.
83. Junquera L. Diagnóstico, prevención y tratamiento de la osteonecrosis de maxilares por bifosfonatos. Recomendaciones de la Sociedad Española de Cirugía Oral y Maxilofacial (SECOM). Rev Esp Cirug Oral y Maxilofac 2008;30:145-156. Disponible en http://www.secom.org/common/view Blog.aspx?ID=860. Última consulta: 13/5/09.
84. Barker K, Rogers S. Bisphosphonate-associated Osteonecrosis of the jaws: a guide for the general dental practitioner. Dent Update 2006;33:270-2, 5.
85. Edwards BJ, Hellstein JW, Jacobsen PL, Kaltman S, Mariotti A, Migliorati CA. Updated recommendations for managing the care of patients receiving oral bisphosphonate therapy: an advisory statement from the American Dental Association Council on Scientific Affairs. J Am Dent Assoc 2008;139:1674-7.
86. Migliorati CA, Casiglia J, Epstein J, Jacobsen PL, Siegel MA, Woo SB. Managing the care of patients with bisphosphonate-associated osteonecrosis: an American Academy of Oral Medicine position paper. J Am Dent Assoc 2005;136:1658-68.
87. Felsenberg D, Amling M. Kiefernekrosen nach hoch dosierter. Bisphosphona ttherapie. Dtsch Arztebl 2006;103:3078-81.
88. Khan AA, Sandor GK, Dore E, Morrison AD, Alsahli M, Amin F et al. Canadian consensus practice guidelines for bisphosphonate associated osteonecrosis of the jaw. J Rheumatol 2008;35:1391-7.
89. Lam DK, Sandor GK, Holmes HI, Evans AW, Clokie CM. A review of bisphosphonate-associated osteonecrosis of the jaws and its management. J Can Dent Assoc 2007;73:417-22.
90. Baim S, Miller PD. Assessing the clinical utility of serum CTX in postmenopausal osteoporosis and its use in predicting risk of osteonecrosis of the jaw. J Bone Miner Res 2009;24:561-74.
91. Silverman SL, Landesberg R. Osteonecrosis of the jaw and the role of bisphosphonates: a critical review. Am J Med 2009;122(2 Suppl):S33-45.
92. Solomon DH, Hochberg MC, Mogun H, Schneeweiss S. The relation between bisphosphonates use and nonunion of fractures of the humerus in older adults. Osteoporos Int 2009;20:895-901.
93. Abrahamsen B, Eiken P, Eastell R. Subtrochanteric And Diaphyseal Femur Fractures in Patients Treated with Alendronate: A Register-Based National Cohort Study J Bone Miner Res 2009. PMID: 19113931.