

Review

Adverse effects of bisphosphonates

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ABSTRACT

Aminobisphosphonates are drugs that have been used successfully in the treatment of osteoporosis for more than 20 years. Although main registry studies found a scarcity of relevant adverse events, in recent years and as a result of pharmacovigilance, different complications have been reported, some potentially serious. This has raised questions on the safety of these drugs, especially in high doses, like those used in oncology and long-term treatment, as needed in patients with osteoporosis. In this review, based on the analysis of relevant scientific evidence from clinical trials, case series, cohort studies and databases published to date, we summarize the clinical and epidemiological characteristics of the adverse effects of these drugs.

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Efectos adversos de los bisfosfonatos

RESUMEN

Los aminobisfosfonatos son fármacos que han sido utilizados con éxito en el tratamiento de la osteoporosis desde hace más de 20 años. Aunque en los estudios principales realizados para obtener la aprobación de su comercialización no se registraron efectos adversos relevantes, en los últimos años, y como resultado de la farmacovigilancia, se ha comunicado de manera irregular una serie de complicaciones, algunas potencialmente graves, que han puesto en duda la seguridad de estos fármacos, sobre todo en dosis elevadas como las que se utilizan en oncología y en tratamientos de larga duración, como los que se emplean en la osteoporosis. En la presente revisión, basada en el análisis de las pruebas científicas más relevantes procedentes de los ensayos clínicos, series de casos, estudios de cohortes y bases de datos publicados hasta el momento, se resumen las características clínicas y epidemiológicas de los efectos adversos de los bisfosfonatos.

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Introduction

Bisphosphonates (BPs) are bone resorption inhibitor drugs whose chemical structure is relatively simple, as they are formed by two phosphate molecules attached to a carbon atom. They are synthetic analogues of inorganic pyrophosphate but unlike those, whose

central atom is oxygen, they have a bridge carbon atom that provides resistance to gastrointestinal enzymatic hydrolysis. In addition, the two carbon radicals not bound to phosphate are able to link chains of variable structure, which are directly related to affinity for bone and antiresorptive activity of each molecule.^{1,2} Adding an amino group to one of the chains has allowed the synthesis of more potent BPs, which can be used orally by being administered weekly or monthly (alendronate, risedronate and ibandronate) or intravenously (pamidronate, ibandronate and zoledronate).

Their use in osteoporosis was notably increased from 1995 onwards, when alendronate—the first orally active aminobisphosphonate (ABP)—was approved, although in reality they have been used

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clinically for more than 40 years. Currently, they are the reference drugs for osteoporosis and Paget's disease treatment, and are starting to be used widely in oncology. Their widespread use has played a positive role on overall health, as BPs acting together with other non-pharmacological measures have been included among the potential causes for the progressive decrease in hip fracture incidence, which started at the end of the last century.^{3,4}

Although BPs have shown a good safety profile in the main clinical trials carried out to approve their commercialisation, different complications have arisen in the last few years. These complications, observed in clinical practice, have caused uncertainty regarding the safety of these drugs, which fully justifies this review.

Action mechanism of bisphosphonates

At present ABPs are the most commonly used in clinical practice, as they have an extraordinary avidity for divalent cations such as Ca⁺⁺, causing them to be quickly captured from the bloodstream by mineral surfaces under resorption by osteoclasts.⁵ These cells are the main target of their pharmacological action; they internalise the drug by endocytosis and experience enzyme inhibition in the mevalonate pathway–farnesyl pyrophosphate synthase–necessary for isoprenoid formation. These lipid compounds are necessary for the post-translational modification of a series of proteins, including guanosine triphosphatases, whose action on vesicle trafficking and osteoclast ruffled border formation is interrupted. In addition to stopping the above-mentioned metabolic pathway, there is an accumulation of certain precursors, especially isopentenyl pyrophosphate, a product capable of activating a subclass of T lymphocytes, called gamma-delta ($\gamma\delta$) T cells, performing immunoregulatory actions of interest in oncology.

Osteoclasts that have “swallowed” the BP located in the mineralized area suffer a loss of their resorptive function. In diseases such as post-menopausal osteoporosis, characterised by an altered remodelling balance where resorption predominates, this resorptive loss will produce an equilibrium that reaches values similar to those common in pre-menopausal women. We still do not clearly know the fate of osteoclasts “attacked” by BPs. We have recently seen that the number of these cells does not decrease, contrary to what was previously believed, and that their size increases.⁶ The significance of these findings is not known; however, the functional capacity of these giant osteoclasts is seriously affected and they are unable to exert their physiological action.

Adverse effects (Table 1)

Gastroesophageal adverse effects

Shortly after oral BPs were introduced in osteoporosis treatment, adverse effects associated with gastroesophageal mucosa irritation, such as nausea, vomiting and dyspepsia, were observed. The appearance of several cases of oesophagitis and oesophageal erosions in pharmacovigilance studies⁷ brought about the generalisation of preventative measures to reduce the risk of these complications (taking the drug with a 180-240 ml glass of water in an upright position and avoiding lying down until 30 min had elapsed and breakfast had been eaten). Such measures caused their incidence to dramatically decrease.⁸ Currently, 15 years since alendronate commercialisation, and after the introduction of other ABPs into clinical practice, the accumulated scientific studies indicate that the risk of digestive adverse effects is low. However, a slight increase in gastroduodenal ulcer (odds ratio=1.45, CI 95%: 1.31-1.61) and oesophageal events (odds ratio=1.86, CI 95%: 1.49-2.32) has been reported in patients without prior gastroesophageal pathology, with no significant differences between the various products marketed.⁹⁻¹¹

Table 1

Classification of the adverse effects of bisphosphonates

1. Extraosseous adverse effects
Gastroesophageal
Ocular
Renal
Hypocalcaemia
Acute phase response
Atrial fibrillation
Pregnancy and lactation
Miscellany
2. Adverse bone effects
Musculoskeletal pain
Over-suppression remodelling
Atypical fractures
Osteonecrosis of the jaws

In 2009, the FDA reported a series of 23 cases of oesophageal cancer in patients treated with alendronate.¹² A national Danish registry analysis surprisingly showed a lower incidence rate in the control population.¹³ Solomon¹⁴ confirmed these results in observing an oesophageal cancer rate of 0.27/1,000 in Medicare beneficiaries who followed BP treatment, compared to a rate of 0.48/1,000 in patients treated with other anti-osteoporotic drugs. These results were surprising as the profile for irritative effects of the oesophageal mucosa in BPs could be a factor that would increase the risk, instead of reducing it. Currently, we suspect that there is a selection bias that could influence in a certain way according to the methodology used. On the one hand, patients with a history of dyspepsia or reflux would have less probabilities of using BPs and, on the contrary, those using them would have higher probabilities of having an endoscopy, which would increase the cancer diagnosis rate. However, while waiting for more conclusive studies, it is advisable to take precautions in patients with gastroesophageal pathology, as they were excluded in the clinical trials carried out.

Based on the previous considerations, we can conclude that the presence of a recent upper gastrointestinal bleeding history, documented history of active peptic ulcer or Barrett's oesophagus constitutes a contraindication for the use of BP orally. In addition to oesophageal motility disorders (stricture, achalasia and scleroderma), gastric or oesophageal varices or gastroesophageal reflux disease should be considered as relative contraindications and other alternative therapies should be assessed. Finally, if a patient develops dyspepsia related to BP, intravenous application or change of molecule is advised, as continuous proton pump inhibitor use is not recommended because it increases the risk of fractures.¹⁵

Ocular adverse effects

Conjunctivitis is the most common ocular adverse effect, although its real incidence is very low.^{16,17} It generally responds very quickly to topical treatment, even if the drug is continued. However, it is wiser to withdraw the drug, even if only temporarily. Some cases of unspecific conjunctivitis probably have an indirect relationship to BPs that the majority of soaps contain, after contact in personal hygiene use. In any case, conjunctivitis is generally mild and transient, even without treatment.

Another complication that is less frequent but potentially more serious is uveitis.¹⁸⁻²⁷ Its incidence is very low, between 2 and 5 cases

per 10,000 patients treated. Its location is generally anterior, although a single case of posterior uveitis has been described. Its appearance is very variable, with an average 70 days after the start of drug treatment (between 1 and 146) and its incidence is greater in patients treated with intravenous ABPs. It has an unknown pathology, and it has been related to acute phase response provoked by the release of IL-6 by activated $\gamma\delta$ T lymphocytes. An increased susceptibility to uveitis has also been seen in patients with associated diseases, such as spondyloarthropathies, Behcet's syndrome, Wegener's granulomatosis or sarcoidosis, and/or who follow treatment with certain drugs, where BP would act as a precipitating factor.

Over the last 17 years, since the publication of the first case of iritis,²⁸ there have been isolated clinical cases related to BP with a variety of ocular disorders different from conjunctivitis and uveitis: periorbital oedema,²⁹ retinal detachment,³⁰ transient ocular myasthenia,³¹ optic neuritis³² and so forth. Sometimes the association is not well demonstrated and it could be an intercurrent problem not related to the drug. In any case, the clinician should act cautiously with any ocular problem that occurs during BP treatment.

Renal toxicity

Renal toxicity is rare in osteoporosis patients treated with oral BPs and the cases published are anecdotal.³³ However, we cannot say the same about oral BPs used in patients with renal failure, as in clinical trials undertaken this process was one of the reasons for exclusion. According to the FDA, they should be used with caution in patients with creatinine clearance lower than 30 ml/min and we do not have BP usage guidelines for patients with pre-existent chronic kidney disease.

The majority of published renal toxicity cases were reported with the use of intravenous BPs.³⁴⁻³⁶ The most commonly described patterns were acute tubular necrosis and focal segmental glomerulosclerosis. Their real incidence is unknown, although there are various factors that increase the risk of toxicity³⁷: pre-existing chronic kidney disease, diabetes mellitus, hypertension, multiple myeloma, hypocalcaemia, chemotherapy and previous treatment with a BP.³⁸ If any of these processes is present, intravenous BP should be used with caution and should even be contraindicated in certain cases. In addition, we must take into account other renal enhancing risk factors, such as the total cumulative dose, infusion rate and the interval between doses

Taking into account that BPs are frequently used in elderly people, where the incidence of serious commitment of renal function is relatively common (up to 54% in patients with osteoporosis who are over 80 years old), it is advisable to carry out renal function controls before and during oral BP treatment.³⁹ We should also take precautions in patients submitted to intravenous treatment.

Hypocalcaemia

Aminobisphosphonates are potent inhibitors of bone resorption. As a consequence, ABPs can provoke a decrease in circulating calcium levels, especially if high concentrations are abruptly reached, as occurs when they are administered intravenously. Symptomatic hypocalcaemia incidence is frequent in patients treated with intravenous zoledronate,⁴⁰ especially in doses and indications for oncology.⁴¹ This occurs even if proper prophylactic administration of calcium and vitamin D is carried out. This adverse effect is more frequent in patients with risk factors such as previous hypoparathyroidism, vitamin D deficiency and kidney failure. Precautions and post-infusion controls should be taken with these patients. In patients treated with oral BPs, hypocalcaemia is rare and can be seen weeks after the start of treatment.⁴²⁻⁴⁴ As a compensatory mechanism, there is an increase in PTH secretion, which could decrease the effects of BP on bone; we should consequently be sure that there is an proper intake of calcium and

normalise or correct any vitamin D deficiency in all patients before and during treatment.

Acute phase response

Acute phase response (APR) is a reaction that has been known about for more than 20 years,⁴⁵ which occurs in some patients that start ABP treatment.⁴⁶ Clinically, it is characterised by an acute and transient set of symptoms of fever and myalgias that lasts between 1 and 3 days (occasionally up to 7-14 days); the symptoms respond to paracetamol and are cured with no sequelae. The APR reaction is relatively common after the first intravenous preparation infusion (variable incidence, estimated between 10% and 30%), and its occurrence is dramatically decreased in subsequent infusions. It has also been very rarely reported with oral ABPs on weekly and monthly doses, but never with patients treated with non-ABPs (etidronate, clodronate and tiludronate).

The APR mechanism has been partially clarified and seems to be related to the release of tumour necrosis factor alpha and IL-6. However, we still do not know the type of effector cells that release these cytokines and the basal process that causes this response. It is known that $\gamma\delta$ T cells participate in a primary innate immunity, playing an important role in the activation of dendritic cells and their capacity for antigen presentation.⁴⁷ They can also be activated by non-peptide antigens,⁴⁸ among which are natural or foreign phosphoantigens, and also by the accumulation of intermediate metabolites in the mevalonate pathway,⁴⁹ especially isopentenyl pyrophosphate (IPP). When BPs act on this pathway through farnesyl pyrophosphate synthase inhibition, they induce raised IPP production, which is a potent activator of $\gamma\delta$ T cells. After activation of this subclass of T lymphocytes, the dendritic cells mature, which increases their migratory activity; there is upregulation of chemokine receptors and this finally triggers a Th1 immune response.⁵⁰ This specific ABP action has been offset by HMG-Co A reductase inhibitors in experiments *in vitro*,^{51,52} although atorvastatin did not reduce its incidence in a study in children treated with intravenous ABP.⁵³ Recently, in a small sample of patients treated with intravenous zoledronate,⁵⁴ there was an inverse relationship between APR frequency and levels of 25-OH vitamin D3. The pathogenetic and practical scope of this is unknown, but should be investigated in larger series.

Atrial fibrillation

The first observation of this surprising adverse effect occurred when analysing the results of a major clinical trial with zoledronate, administered intravenously once a year for osteoporosis treatment—the HORIZON study.⁵⁵ The patients who received the active drug showed an incidence of atrial fibrillation (AF) defined as "serious" (episode that causes hospital admittance or significant morbidity), higher than that of the placebo group (absolute risk: 1.3% against 0.5%; $P < .001$), although the overall incidence was no different between the two groups. Upon observing this finding, various studies were set up to try and clear up its importance. In a retrospective analysis⁵⁶ of the main clinical trial for alendronate (Fractures Intervention Trial), an insignificant statistical increase was seen of the incidence of "serious" AF in the group treated with alendronate (RR=1.51, with a CI 95% of 0.97-2.40).

In an observational study carried out in Denmark,⁵⁷ where a sample of about 13,000 patients with AF was included with more than 60,000 controls, the authors did not see a significant AF risk related to oral BPs (specifically etidronate and alendronate). However, in a smaller-scale study of cases and controls⁵⁸ carried out in the United States that focused on only alendronate, there were differences quantified in an incidence of 6.5% in patients treated with oral alendronate compared to 4.1% in the control group; this adjudicated a relative risk expressed as a odds ratio of 1.86 (1.09-

3.15). A possible explanation of the HORIZON events is that AF was produced by pro-inflammatory cytokine release (in a way similar to flu-like symptoms) or by transitory hypocalcaemia after the infusion. However, a later analysis of the facts showed that the majority of AF cases occurred several months after the infusion and the ECGs performed on 559 patients before and 11 days after showed no difference between the groups.⁵⁹ Currently, while awaiting more complete data, the FDA has indicated that it considers the AF risk with BP is very low, if it exists, and the benefits of treatment clearly outweigh the risks.⁶⁰ Given that the overall incidence of episodes does not differ from that in the placebo group and differences have only been observed in the appearance of serious episodes, it is suspected that BPs do not trigger AF but could aggravate a pre-existent disorder. This is why we advise extreme vigilance in patients at risk and a radial pulse control should be undertaken before prescribing BP and during clinical follow-up (and if this is irregular, an ECG should be performed). It is not necessary to modify the rest of the current clinical practice patterns.

Musculoskeletal pain

Although this was a known fact by clinicians and had been published in some series,^{61,62} the appearance of this adverse effect did not take on a relevant role until 2008, when the FDA⁶³ published a warning indicating the possibility that bone, joint and/or muscular pain could appear in patients treated with BP, which could be occasionally incapacitating. Symptom onset begins in a very variable manner, from the first days of treatment to months or even years afterwards. Drug withdrawal is usually enough to control the pain; although in some patients recuperation is slow, it is rarely incomplete.⁶² This adverse effect should not be confused with acute phase response, where (in addition to arthromyalgia) there are also some other flu-like symptoms, such as shivering and fever, that completely disappear after two or three days even if treatment is continued.

Musculoskeletal pain has been described with alendronate and risedronate, with a very low incidence, but unknown until now. It is more frequent with weekly doses and much rarer with daily ones, which suggests that the treatment with low daily doses initially could "sensitize" the patient and avoid the appearance of pain.⁶³ However, a recent study carried out by researchers at the Mayo Clinic,⁶⁴ where a numerous cohort of patients was included, did not show a significant increase of musculoskeletal pain related to BP. This was after taking into account the numerous confusing factors that could influence the appearance of a symptom so prevalent in the target population of these drugs.

Despite the fact that data reported are confusing, we should be careful when pain appears in patients treated with BP. Many pathogenic factors can arise and they should be controlled. For example, various cases of synovitis associated to BP use have been described^{65,66} and a case of polyarthritis⁶⁷ has been confirmed with re-exposition to the drug. Patients with vitamin D deficiency submitted to BP treatment can frequently suffer from concomitant osteomalacia that presents with pain and can worsen if not treated with sufficient doses of vitamin D. Finally, the appearance of acute pain in the thighs could be the initial symptom of a femoral stress fracture that could evolve into a shaft fracture if proper measures are not taken. Consequently, the appearance of recent-onset musculoskeletal pain in patients treated with BP is a rare but relevant event, which should be taken into account for the necessary diagnostic and therapeutic measures to be taken.

Atypical fractures of the femoral shaft

The first cases were published in 2005.⁶⁸ In this article, there was a series of 9 non-selected patients who had been treated or were having

long term treatment with alendronate. The histomorphometric study showed a marked suppression of bone formation on trabecular surfaces, with a very small number of osteoblasts and matrix synthesis markedly reduced. This alteration was evidenced by the virtual disappearance of the lines double marked with tetracycline in all patients. Osteoclastic surfaces and surfaces of erosion were also well below normal. There were similar findings in endocortical and intracortical surfaces. This histological pattern of "severely suppressed bone turnover" was similar to that observed in the adynamic bone disease that occurs in some patients undergoing prolonged haemodialysis.⁶⁹

Since then there have been various isolated cases and a series of cases from retrospective studies,⁷⁰⁻⁷⁴ which were characterised by frequent pain in the thigh before fracture; this suggests that they could be preceded by stress fissures whose cure was decreased due to the low exchange.⁷⁵ In addition, we identified a specific radiographic pattern characterised by hypertrophic corticals, which was also seen in the contralateral femur in some cases.⁷⁶ The fracture line was transverse or oblique (Figure) in contrast to oligo-traumatic shaft fractures occurring in elderly, which are usually spiral and chipped. However, the incidence of this possible BP treatment complication is very low, estimated at 7.8 per 100,000 people per year for patients over 60 years old. These results were confirmed in a recent analysis combined with the FIT, FLEX and HORIZON clinical trials, with no relevant significant increase being confirmed in any of the 3 studies.⁷⁷

We can conclude that femoral shaft fractures related to BP are very rare and do not affect the known benefit-risk relationship of these drugs when used in patients with established osteoporosis. However, clinicians should take care when pain appears in the thighs during long-term treatment, and should perform x-rays to rule out stress fractures. Although more studies are necessary to definitely clear up the problem, we also consider it wise to suspend treatment if there is an atypical femoral fracture and assess the prescription of all other drugs, as well as anabolic therapies.

Osteonecrosis of the jaws

Since the FDA received the first reports in 2002 on osteonecrosis of the jaw (ONJ) in cancer patients treated with ABP,⁷⁸ the number of articles published in medical journals⁷⁹⁻⁸² and also in general newspapers has increased exponentially and its social impact has transcended the specialized environment, making it difficult to make decisions based on the reality of scientific tests. In 2007,⁸³ a working group set up by the American Society for Bone and Mineral Research defined ONJ as the "the presence of an exposed bone in the maxillo-facial area that does not cure after 8 weeks of being identified by a health professional, in a patient who follows treatment or is exposed to BPs and has not received radiotherapy in the area." The group also pointed out that the incidence of this adverse effect is rare in patients with osteoporosis and Paget's disease, being between 1/10,000 and 1/100,000 patients per year of treatment. Although having a definition contributed to focusing on the problem, the inclusion of BP as a compulsory fact is a mistake from the epidemiological point of view, as the risk factor is included (that is, the BP) as a requirement for the outcome. This problem, added to the previous absence of a specific ICD-9 code, has kept the incidence of the non-exposed subjects from being known, an essential fact to really know the impact of drug exposition.⁸⁴ In cancer patients treated with high intravenous BP doses, the risk is much more evident, with a much more variable incidence being estimated as summarised in Table 2.

We find ONJ more often in the jaw (65% of cases) and two thirds of patients have a history of tooth extraction, implant or other type of oral surgery, with the rest of cases being due to spontaneous appearance. The onset of symptoms is usually insidious, with little

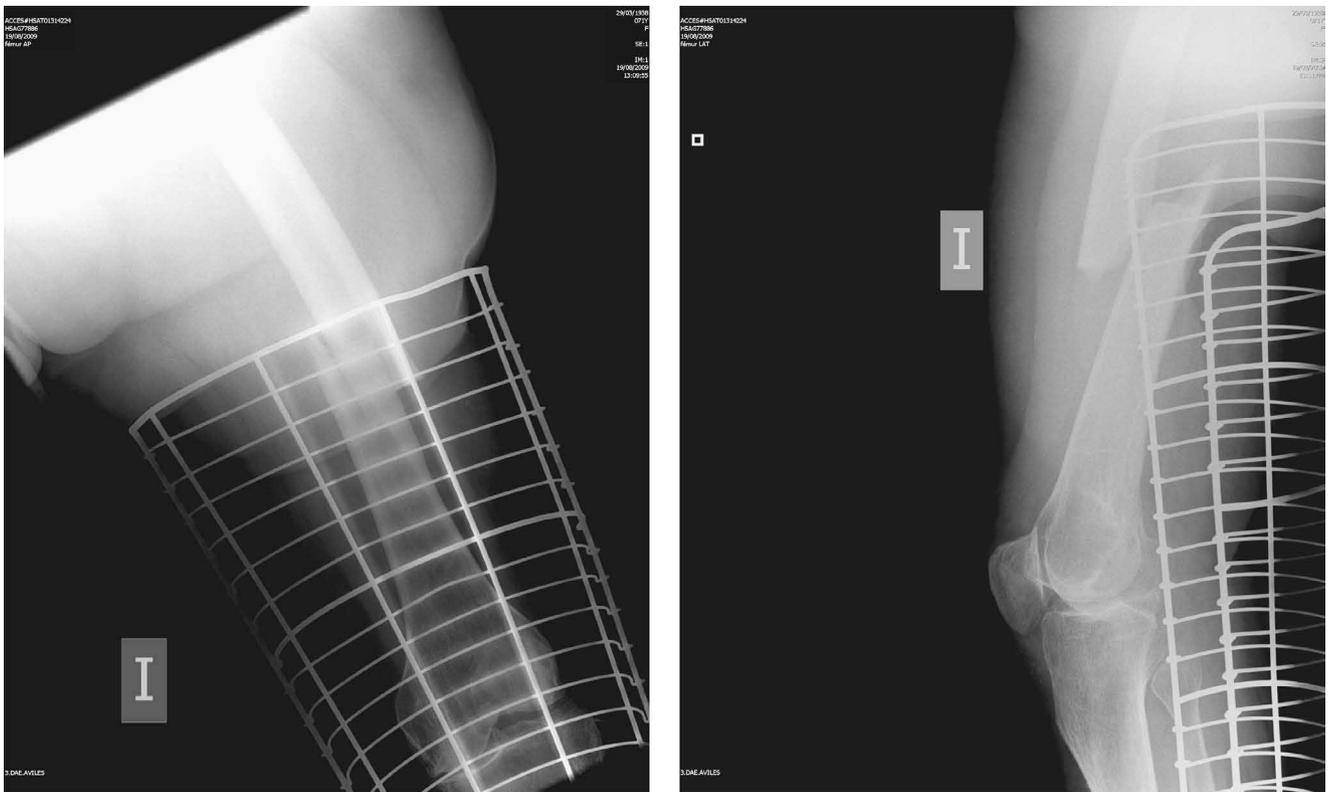


Figure. Characteristic radiographic pattern of an atypical femoral diaphysis fracture in a 70-year-old female treated with long-term aminobisphosphonates.

or no pain, although as time goes by there is usually pain in the area and even general manifestations such as fever and general symptoms that are difficult to control.⁸² The exact factors for developing ONJ are unknown, but in published series a greater incidence is observed in patients with periodontal disease or bad oral hygiene, lack of teeth and repeated local trauma due to badly fitting prostheses. The presence of advanced neoplasms and oncological treatments, including corticoids, without a doubt constitute factors that should be taken into account to assess ONJ risk and to establish proper preventative measures. As for associated drugs, some characteristics

such as antiresorptive potency (zoledronate is the most potent and the one with which more cases have been described) and long-term treatment, are associated with an increase in risk.⁸³

The diagnosis is carried out with a visual inspection, observing lesions that could be lytic, sclerotic or mixed and could spread to adjacent soft tissues, frequently associated with super-infection. A simple x-ray generally provides little information and it is necessary to carry out other studies, such as magnetic resonance and gammagraphy, to confirm the existence of ONJ and assess its spread and characteristics. It is essential to rule out other processes that

Table 2
Incidence of osteonecrosis of the jaw associated with bisphosphonates

Drug	Indication	Type of study	No.	Cases, %	Reference
BP IV	MM	Descriptive	554	6	Hoff, 2008 ⁹⁵
BP IV	MM	Descriptive	80	28	Boonyapakorn, 2008 ⁹⁶
BP IV	MM	Cohorts	1,621	8.5	Vahtsevanos, 2009 ⁹⁷
BP IV	Breast cancer	Cohorts	1,621	3.1	Vahtsevanos, 2009 ⁹⁷
BP IV	Breast cancer	Descriptive	75	5.3	Walter, 2009 ⁹⁸
BP IV	Prostate cancer	Cohorts	1,621	4.9	Vahtsevanos, 2009 ⁹⁷
BP IV	Prostate cancer	Clinical trial	60	18.3	Aragon-Ching, 2009 ⁹⁹
BP IV	Breast, colon and renal cancer	Descriptive	3,560	0.9-2.4	Guarneri, 2010 ¹⁰⁰
BP IV	Osteoporosis	Descriptive	622	0	Jung, 2010 ¹⁰¹
Oral BPs	Osteoporosis	Postal survey	8,572	0.1	Lo, 2010 ¹⁰²
Oral BPs	Osteoporosis	Postal survey		0.01-0.04	Mavrokokki, 2007 ¹⁰³
Oral BPs	Osteoporosis	Descriptive	208	4	Sedghizadeh, 2009 ¹⁰⁴

BP indicates bisphosphonate; IV, intravenous; MM, multiple myeloma; N, number of cases.

could cause similar symptoms, when dealing with bone radionecrosis in patients who have undergone head and neck radiation therapy and dealing with jaw metastases.⁸⁵

The pathogeny of ONJ is unknown. One of the theories involved, derived from BP antiresorptive capacity, suggests that an excessive suppression of the remodelling would cause microfractures, osteocyte apoptosis and necrosis of the matrix.⁸⁶ The alveolar bones are places of high turnover, where (at least in theory) large quantities of BPs will be deposited, especially if used in high doses and/or for long periods. In the jaws of dogs treated with zoledronate, suppressed cortical remodelling and accumulation of non-viable osteocytes have been observed, with areas of necrosis of the matrix. These are findings that could contribute to delay in healing and development of infections after tooth extraction.⁸⁷ Other mechanisms that have been considered would be the effects of BPs on keratinocytes⁸⁸ and on angiogenesis.⁸⁹ In a Murine model⁹⁰ developed recently that quite closely mimics the clinical and histopathological picture that occurs in humans with myeloma treated with high doses of intravenous BP, it has shown that antiresorptive synergistic action with the formation of multinucleated giant osteoclasts, and antiangiogenic drugs may be responsible for the appearance of lesions. This is a process enhanced by combination therapy with immunosuppressants and cytostatics. The development and study of this first animal model could provide the keys to the pathogeny and treatment that will allow an approach to the complication.

Currently, a great number of scientific societies and regulatory agencies have created their own recommendations that generally coincide in their basic aspects. The Spanish Agency for Medications and Health Products recommends in its information sheet 2009/10⁹¹ some preventative measures that will be stratified according to patient risk and that are summarised below:

1. It is important to decide to start BP treatment once the benefits (prevention of fractures due to bone weakness) and individual patient risks are assessed, taking into account that it is normally a long-term treatment, a situation that could be a risk factor for ONJ.
2. The recommendations in the current clinical guides published by the respective CC health services and scientific societies should be taken into account.
3. Once the need for BP treatment is decided, the following preventative dental measures should be undertaken:
 - An initial assessment of the patient's oral health state and regular dental revisions should be carried out. Patients should also go to the dentist as soon as any symptoms, such as oral pain or inflammation, occur.
 - When dental interventions are necessary, these should be as conservative as possible (maintaining the piece).
 - If extractions or invasive procedures are needed, it is recommended that the dentist refer the patient to centres that are experienced with this type of patients.
 - Patients who develop ONJ should receive the appropriate treatment by professionals with experience in this pathology.
4. So that these recommendations can be effectively applied, it is essential that local Guidelines and Protocols be developed and shared by the different areas and care levels involved in the patient's follow up.

These recommendations are useful and based on common sense. However, they do not respond to some specific relevant aspects for clinical practice. The first of these is whether BP treatment should be stopped. Although there are no scientific tests that indicate that drug withdrawal improves process evolution, it is wise to opt for

the potentially safest option, which would be drug withdrawal and assessing the possible indication of another treatment. In the case of non-neoplastic osteoporosis, this could be an anabolic or mixed action PTH (such as strontium ranelate), drugs that have a different action from BPs and that have not had any recorded ONJ cases up to now. In patients without ONJ who are going to undergo an invasive dental procedure such as an extraction or implant, the decision is less clear. Some authors recommend drug suspension for several months before and starting it up again several months after the surgical wound has healed. In this way the remodelling would be partly recovered and the ONJ risk would be reduced. However, we also lack scientific tests that can vouch for this decision and the protective mechanism invoked is not sustainable as the BPs remain for long periods in the bone tissue, maintaining their antiresorptive capacity. The decision to temporarily suspend BP, in the opinion of these review authors, should belong to the doctor, who will assess the risk of fracture or neoplastic disease progression, and the consequences of the withdrawal. Another aspect that has caused controversy is the use of ONJ risk markers in making decisions. It has been proposed that values above the pre-established threshold of CTX (C-terminal telopeptide of procollagen type I) are associated to a greater risk of ONJ.^{92,93} However, determination of this marker is subject to biological variability, which depends on various factors; its levels are generally low in patients treated with BP and with other antiresorptive agents, who are never going to develop ONJ.⁹⁴ These facts, added to the lack of scientific tests vouching for this determination as a guideline to suspend or maintain the treatment, reasonably advise against its use in clinical practice.

Pregnancy and lactation

The safety of BPs in pregnancy and lactation has not been sufficiently studied because the majority of patients treated are at a postmenopausal stage. However, there is the possibility of prescribing them to fertile women (pre-menopausal osteoporosis of any nature, osteogenesis imperfecta, etc.), which is why the precise situation of this problem should be known.

It is not known whether there is transplacental passage of BP or whether it affects fertility. Up until now, and in therapeutic doses, teratogenicity has not been observed in humans or animal models, although one study showed a reduction in bone growth and foetal weight in rats exposed to BP during pregnancy.¹⁰⁵ Several cases of BP use in pregnant women have been reported where transient hypocalcaemia occurred in the newborn without clinical relevance.¹⁰⁶ Lastly, there have been no reports of BP passing to the maternal milk¹⁰⁷ and no adverse effects have been seen during this period, although the studies are very scarce and should therefore be used with caution. The FDA classifies BPs in the Group C risk group (textually defined as: "we do not have information on humans but a risk has been observed in studies carried out with animals or such studies have not been carried out"). However, EULAR recommends their withdrawal six months before the pregnancy (with an evidence level 4), which establishes the need to use safety protocols in pre-menopausal women, in a manner similar to that used with methotrexate and drugs with a similar profile.¹⁰⁸

Miscellany

Slight cutaneous reactions have been reported, such as rash or itching, which occur with a frequency similar to that seen with antibiotics and stop without side effects upon drug withdrawal. However, cases of serious processes such as Stevens-Johnson syndrome are very rare.¹⁰⁹ There have also been isolated cases of mild hepatotoxicity^{110,111} that ceases after the drug is withdrawn and are characterised by a slight increase in transaminases at the start of treatment. In large databases, a collection of various

adverse effects produced anecdotally have been collected (asthenia, headache, vertigo and dysgeusia) and it is very doubtful that they are attributed to BP.^{112,113}

Conclusions

The general profile of BP safety is acceptable and its adverse effects are usually mild. However, in the last few years and because of pharmacovigilance and analysis of state databases, a series of complications related to these drugs have been reported. These could be serious and knowledge about them on the part of clinicians is essential to make proper decisions in each case.

Gastrointestinal adverse effects are frequent although they rarely constitute a reason to withdraw treatment. However, in cases where problems persist after checking that the BPs are being taken correctly, the prescription of long-term antisecretories should be avoided due to their negative bone mass effect and incidence of fractures. In addition, a change of the way the BP is administered or its therapeutic class should be considered. Acute phase reaction, the most common adverse effect related to intravenous BPs, responds well to paracetamol and tends to disappear with subsequent infusions. We must also remember the need to ensure a good supply of calcium and vitamin D to avoid post-transfusion hypocalcaemia, especially in patients at risk. Other effects such as musculoskeletal pain, kidney damage and hepatotoxicity are very rare and would rarely cause drug withdrawal.

The two most controversial side effects are currently osteonecrosis of the jaw and atypical fractures of the femoral shaft. Although the pathogeny of these processes is not known, it is necessary to take precautions in both cases, especially in high risk patients. Likewise, BP indication should be carefully assessed, avoiding its administration if the risk of fracture is not high and assessing its withdrawal or temporary suspension after 5 years of treatment.

Conflict of interest

The authors declare no conflict of interest.

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