BISPHOSPHONATE-ASSOCIATED OSTEONECROSIS OF THE JAW.

Presentation of 15 cases

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INTRODUCTION

Bisphosphonates (BPs) are synthetic analogues of the naturally occurring inorganic pyrophosphate, with a high affinity for calcium. Because of this characteristic, BPs are deposited into the mineralized bone matrix for long periods of time [1]. All of the BPs share a common chemical structure, consisting of a carbon atom bond to two phosphate groups (P-C-P), whose negative charge accounts for the high affinity of these molecules for the bone tissue. Their potency of action is based on the side chains bound to the nucleus. The presence of nitrogen compounds in these chains confers higher activity to the BP molecule [2].
Although their action mechanism is not completely understood, it is known to be based on the ability of the BP molecules to bind hydroxyapatite, thus inhibiting osteoclastic bone resorption without interfering with bone formation and mineralization [3]. The antistereoclastic effect is thus a consequence of both: arresting the differentiation of common precursor cells (hematopoietic stem cells) and promoting apoptosis of mature osteoclasts [2]. Furthermore, BPs antagonize bone calcium release induced by tumor cell-produced stimulating factors [3]. These actions may potentially contribute to inhibit bone resorption and to improve bone mass [11]. Certain BPs, particularly the most recently developed and potent ones, which incorporate nitrogen into their molecular structures, have inhibitory effects upon tumor cell proliferation and angiogenesis [3,4].

Intravenous (IV) BPs are primarily used for treating oncologic patients – including patients with hypercalemia of malignancy or bone metastases in the context of solid tumors such as those of breast, prostate or lung cancer – and for managing lytic lesions in the setting of multiple myeloma [5-9]. They are effective in preventing and reducing skeletal complications such as severe bone pain, fractures, or compression of the spinal cord [10]. Although not found to improve survival of oncologic patients, these drugs substantially enhance their quality of life, particularly that of patients with advanced cancer involving the skeletal system. [11]. In August 2007 the US Food and Drug Administration approved the use of a single annual dose of zoledronic acid (Aclasta®) to treat post-menopausal osteoporosis [12-13].

Orally administered BPs are poorly absorbed (below 1%; even less if the patient has failed to fast) and have about 1 hour half-life in plasma, with stable incorporation into bone of about 20% of the absorbed dose. Their half-life in bone is longer than 10 years and they are excreted unmetabolized with the urine [2]. They are primarily indicated to treat osteoporosis [14-15] either emerged in the context of other diseases such as inflammatory bowel disease or primary biliary cirrhosis, or resulting from medication (most commonly steroids) or menopause [16]. Furthermore, they are used to treat a variety of less common conditions such as Paget’s disease of bone, and osteogenesis imperfecta of childhood [11].

In 2003, a newly emerging complication of BP therapy, undetected in previous clinical trials, was described for the first time [17]. This complication, called osteonecrosis of the jaw (ONJ), is now defined by the presence of exposed bone in the mouth which fails to heal after appropriate intervention over a period of 6 or 8 weeks. In the early stages, no radiographic manifestations can be seen. Patients are usually asymptomatic but may develop severe pain because the necrotic bone becomes secondarily infected after being exposed to the oral environment. The osteonecrosis is often progressive and may lead to extensive areas of bony exposure and dehiscence. This condition appears to be caused by a combination of deficient vascular supply and deficient bone remodeling and regeneration. Its onset has been associated to risk factors such as: cancer diagnosis, concomitant treatments (chemotherapy, head and neck radiotherapy or corticosteroid therapy) and situations of comorbidity (anemia, coagulopathy, infection, preexisting oral disease) [18].

These findings suggest that underlying associated circumstances could determine the development of this condition in some patients while not in others. Here we describe and evaluate 15 cases of BP-treated patients who developed ONJ with the aim of gaining deeper insight into this recently emerging entity, by analyzing what are the diseases where this complication most frequently occurs, the age of onset, the BP-type most frequently inducing ONJ, the possible dose- or time-dependency, the clinical manifestations, the current treatment strategies and the possible benefits of discontinuing BP treatment upon onset of ONJ.

**MATERIALS AND METHOD**

This study involved evaluation of patients with clinical signs compatible with ONJ, who were referred to the Service of Stomatology and Oral and Maxillofacial Surgery, of the University Hospital-Maternity Ward of the Grand Canary Island, between September 2006 and October 2007. These patients had been referred from the Departments of Oncology Hematology, Bone Metabolism or Palliative Care of the University Hospital-Maternity Ward.

Patients were selected according to the criteria established by the American association of Oral and Maxillofacial Surgeons (AAOMS) [19]: 1. Patient under current or previous BP treatment; 2. Exposed necrotic bone in the maxillofacial region persisting for more than 8 weeks; 3. No previous history of radiation therapy to the jaws. Patients with neoplastic involvement of the maxillae were excluded.

The information was prospectively gathered through interviews and clinical examinations previous to complementary tests and review of the medical records. Data on the type of BP used, route of administration, co-morbidities, clinical presentation, underlying diseases and results of diagnostic tests were recorded.

**RESULTS**

The study included a total of 15 patients: 12 women (80%) and 3 men (20%), aged 60 years on average (range 41-82) with the following underlying diseases: osteoporosis in 2 patients (13,3%); rheumatoid arthritis in 1 patient (6,6%); and oncologic diseases in 12 patients (80%) who were under anti-neoplastic treatment, some of them (66,6%) also under concomitant treatment with intermittent steroid cycles. The oncologic patients included cases of: breast cancer (40%), multiple myeloma (13,3%), rectal cancer (6,6%) and prostate cancer (13,3%). One of them (6,6%) had coexisting prostate cancer and multiple myeloma (Table I).

The administered BPs and corresponding average doses were as follows: 9 patients (60%) were treated only with zoledronic acid (Zometa®), in an average total dose of 95,5 mg (range 56-132); 3 patients (20%) were treated only with oral alendronate sodium (Fosamax®) in an average dose of 25.350mg (range 8.960-51.970); 2 patients (13,3%) were treated with pamidronate disodium (Aredia®) in an average dose of 1.935 mg (range 1.080-2.790), subsequently substituted by zoledronic acid, in an average dose of 140 mg (range 136-144); and 1 patient (6,6%) was treated with zoledronic acid in a dose of 64mg, subsequently substituted by ibandronic acid (Bondronat®) in a dose of 19.500mg. The mean duration of treatment was 29.8 months (14-65) for
patients under IV BP administration and 87 months (32-176) for patients under oral BP administration. Patient nº 10 received IV and oral BP treatment for a total of 29 months (16 and 13 months respectively).

We found 10 patients (66.6%) with a history of one or more exodontias. However, no known triggering factors could be identified in the 5 remaining patients.

The average time elapsing between the beginning of BP treatment and the onset of ONJ was 21 months (range 16-28) for patients who had not undergone previous dental treatment. All these patients were under zoledronate treatment, discontinued due to ONJ onset. Only one patient continued with BP therapy with ibandronate for 13 additional months after being diagnosed with ONJ. The average duration of ONJ in these patients was 21 months (range 11-43).

The most frequent location of the ONJ lesions was the posterior lingual region of the jaw; we found 11 such cases (73.3%), one of them (9%) also with maxillary involvement. We found only 4 cases (26.6%) of maxillary involvement alone. ONJ was unilateral in 14 cases (93.3%) and bilateral in only one case (6.6%).

Bone density alterations were detected in 9 patients (60%) by spine and hip bone densitometry; these included 6 patients diagnosed with osteopenia and 3 diagnosed with osteoporosis. We found pathological vertebral fractures in 40% of patients in spite of being under high BPs doses.

### Table I. Case descriptions

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<th>Adm route</th>
<th>Dose (mg)</th>
<th>Frequency (days)</th>
<th>Total dose administered (mg)</th>
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### Table II. Personal background. Habits. Concomitant factors.

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**Values in Table 2:**

- Smoking: 0 No 1 yes - 2 Former smoker
- Alcohol consumption: 0 No 1 Habitually 2 Occasionally 3 Formerly
- Exercise: 0 No 1 Reduced (<30' per week) 2 Moderate (30'-60' per week)
- Dairy: 0 < 1200mg Ca/day 1 ≥ 1200mg/day
- Calcium supplementation: 0 No 1 Yes 2 Ca+ vitamin D
- Previous treatment for osteoporosis: 0 No 1 yes
- Pathological vertebral fracture: 0 No 1 yes
- Diabetes: 0 No 1 Type-I 2 Type-II
- Steroids: 0 No 1 yes

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Type II diabetes mellitus had been previously diagnosed to 6 patients (40%). Smoking habit was present in 7 patients (46.6%), who used to smoke a mean of 15 cigarettes/day (range 5-30) for a period of 23 years (range 14-30) on average (Table II).

Regarding the initial ONJ symptom, 9 patients (60%) reported pain, 3 patients (20%) reported inflammation and 3 patients (20%) reported exposed bone into the oral cavity. The most frequently observed symptoms were: ulcerated mucosa with exposed bone (100%) (Figure 1), suppuration (73.3%), halitosis (73.3%), pain (53.3%), altered sensation in the jaw (46.6%), eating disorders (46.6%) and bone loss (46.6%). Our case series included 3 cases (20%) of submental fistulae (Figure 2) and 3 cases (20%) of oronasal fistulae and maxillary sinusitis (Table III). The most frequent findings upon examination were: ulcerated mucosa and exposed bone (Figure 3), with suppuration as a consequence of secondary infection (60%).

Biopsy had been performed in 5 cases (33.3%), where the results showed tissue with non-specific signs of chronic and acute inflammation, no evidence of neoplastic signs, and microorganisms whose morphology was suggestive of Actinomyces.

Ortopantomography had been performed in all of the patients and the results mainly showed ONJ-related osteolysis (Figure 4).
Bone gammagraphy had been performed in 11 patients (73.3%), with rather unspecific results only showing hypercapitation areas (Figure 5).

The therapeutic approach was conservative, with continuous or intermittent cycles of oral systemic antibiotics and mouthwash with chlorhexidine 0.12% for all patients. The most frequently used antibiotic treatment was amoxicillin/clavulanic acid (80%).

Sequestrectomy with mucous flap of the bed was performed in one patient (6.66%); however, this patient again needed sequestrectomy and partial ostectomy of the alveolar process of the mandible two years later. In spite of this, the patient again had exposed bone at the moment of writing this study.

Three patients (20%) with submental fistulae underwent local cures – according to our cure-protocol (20) – with saline solution, ciprofloxacin and hidrogel (Nu-gel®). All of them showed total remission of the fistulae, improvement of their clinical signs, and reduction of feeding difficulties, after 2-3 weeks of treatment.

By the end of this study, 3 patients (20%) showed noticeable clinical improvement and reduction of oral lesions and they were no longer under treatment; 9 patients (60%) still had symptoms, with periods of improvement, depending on the treatment cycles; and 3 patients (20%) had died as a consequence of their underlying diseases.

**DISCUSSION**

The first described cases of IV BP-treated patients presenting with non-healing exposed jawbone were reported in 2003 [21,22]. At present, the actual incidence of ONJ is not known. Published studies are retrospective and conducted with restricted sample sizes, most of them consisting in single-case reports. Cumulative estimations of the incidence of ONJ are about 0.8-12% for IV BPs [23,24] and between 1/10.000 and < 1/100.000 exposed persons per year for oral BPs [25]. Evidence shows that the risk of developing ONJ is significantly higher for patients under IV BPs than for those under oral BPs. However the incidence is expected to increase, as more effective diagnosis techniques are developed, better follow up protocols are implemented, and patient exposure to BP treatments becomes more prolonged.

Although other diagnosis criteria are available, we chose those of the AAOMS [19] because they refer both to IV and oral BP treatments.

BPs mechanism of action is still unclear. These drugs are selective inhibitors of osteoclastic actions in the bone remodeling cycle. Due to their antiresorptive action, BPs reduce bone remodeling and, by accelerating secondary mineralization, they induce a fast detectable increase in bone mineral density [12]. Additionally, they seem to have an effect on osteoblasts by reducing apoptosis and stimulating the secretion of inhibitors in the recruitment of osteoclasts [26]. Antiangiogenic effects have also been described, by inhibiting endothelial cells, reducing their proliferation and inducing apoptosis [4].

Since these drugs inhibit bone resorption and are used to prevent and to treat skeletal complications, their relationship with ONJ is difficult to explain. The fact that maxillary bones are subject to higher bone remodeling and in direct contact with the mouth septic environment could partially account for this outcome [27]. However, establishing a causal relationship requires further research based on prospective randomized double-blind controlled clinical trials [18].

In our 15-patient sample, the age range was 41-82 years with an average of 60, similarly to other published case series [24, 28, 29]. However, we found higher ONJ incidence among women (80%), while other published series reported higher incidence among men [24,2, 8, 30].

Although most ONJ cases are associated to IV BPs such as zoledronic acid – used in 80% of our cases – the occurrence of ONJ associated to oral BPs such as alendronate, ibandronate or risendronate, is being increasingly reported in the literature and was also found among our cases (20%) [22].

Similarly to other published case series [27, 29, 31] the most frequently occurring primary diagnosis in our series was breast carcinoma (40%).

Regarding the time of exposure, significant risk of suffering ONJ seems to appear at about 12-14 months of IV BP treatment and to rise after 36 months [18, 26]. These findings lead to recommendations such as the Mayo Clinic guidelines on the use of BPs, where is it advised to discontinue BP therapy after 2 years for patients in a stable phase of their disease or to decrease it every 3 months for patients whose disease remains active [9].

Development of ONJ with oral BPs requires longer treatments and higher doses, because of their poor bioavailability. The risk increases after 3 years of treatment and it would be wise to restrict chronic treatments to a maximum of 5 years [32]. After that time, patients should go on with general measures (balanced diet, moderate exercise, calcium and vitamin D supplementation and quitting smoking). Alternatively, patients may be treated with intermittent administration schedules or with alternative treatments, if the risk of suffering fractures remains high [32].

The most frequent maxillary localization of ONJ lesions was on the jaw (73,3%). The higher involvement of maxillae – as compared with other bones – may be influenced by the fact that they are linked to the teeth through the periodontal ligament, which facilitates the spread of odontogenic and periodontal infections. Other anatomical factors that may promote maxillary involvement are: thinness of the mucosal coating of maxillae – which makes it susceptible to trauma and ulcerative lesions that establish a communication via between mouth and bone – and the terminal vascularization-type of the jaw [33].

Exodontia was the most frequently found related event in our patients’ medical records (66,6%). Other published series have reported from 33% [27] to 86% [22] previous exodontias. Further associated risk factors have been reported, such as smoking habits and diabetes (34, 35). Thus, smoker or diabetic patients, as well as patients under concomitant corticoid or anti-neoplastic treatment should be evaluated in more detail. However, cases of spontaneous ONJ onset also occur. In our series, such cases amounted to 33,4%.

In our study, only one of the patients with ONJ associated to oral BPs was under concomitant corticosteroid treatment. This patient presented with ONJ after 32 months of treatment, with onset after a tooth extraction without antibiotic prophylaxis.
Apstrakt

Uvod: Osteonekroza vilica (ONV) je novootkrivena komplikacija bifosfonatne terapije (BP), prvi put opisana 2003, koja nije zapažena u ranijim kliničkim ispitivanjima. Cilj ovog istraživanja bila je evaluacija kliničkih karakteristika kod 15 pacijenata sa osteonekrozom vilica povezanim sa terapijom bifosfonata da bi se postigla bolja strategija lečenja.

Metod: U ispitivanje je uključeno 15 pacijenata sa osteonekrozom vilica izabranih prema kriterijumima Američke asocijacije oralnih i makillofacijalnih hiruraga. U studiji su analizirani: tip bifosfonatne terapije, put inošenja bifosfata, komorbiditet, kliničko ispoljavanje i rezultati dijagnostičkih testova.

Rezultati: Ispitivano je 12 žena i 3 muškarca, srednja starost bila je 60 godina. Od njih 15, troje je bilo sa oralnom terapijom bifosfata, a 12 sa intravenskom terapijom. Prosečno trajanje lečenja iznosilo je 29,8 meseci sa intravenskom i 87 meseci sa oralnom bifosfonatnom terapijom. Većina analiziranih slučajeva bila je uvezena sa upotreom zoledronata (80%). Karcinom dojke bio je najčešći prateći uzrok (40%). Vilica je bila najčešća lokalizacija osteonekroz (73,3%), a egzodoncija zuba najčešći trigering faktor (66,6%).


Due to the complexity of the treatment and the uncertainty of the results, prevention and patient information should be the primary objectives.

CONCLUSIONS

The osteonecrosis of the jaw is a condition that affects mainly to patients in advanced ages – 60 years on average – and is more prevalent in women. It is important to individualize each patient by evaluating the administered BP, route of administration – IV or oral – duration of treatment, administered doses, primary disease and possible concomitant diseases or treatments. We observed a direct relationship with the time of exposition to BP and the accumulated dose. Zoledronate seems to be the BP most frequently associated to ONJ, probably because it is the most potent and most frequently used one for IV administration.

Jaw is the most frequent location for this condition (73,3%). From all known triggering factors, previous exodontia appears to be the most strongly related one. ONJ diagnosis is mainly based on clinical findings without the need for complementary tests or biopsy.

The treatment depends on the characteristics and progression of every individual case. Prevention is the best approach to this condition. Providing correct information to patients and coordinating medical and dental assistance seem to be essential for preventing it.
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