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POSSIBLE ORAL CAVITY IMPLICATIONS OF BISPHOSPHONATES THERAPY

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Osteoporosis is a condition with a major impact on health. According to the World Health Organization (WHO) criteria, osteoporosis is defined as a bone mineral density (BMD) that lies 2.5 standard deviations (SD) or more below the average value for young healthy women. The morbidity of osteoporosis is generated by the fractures that may occur. Treatment with bisphosphonates is considered as the primary line therapy. Numerous meta-analysis have highlighted the efficacy of tratment with bisphosphonates for fracture risk in patients with osteoporosis. Systematic studies or reviews reported atypical fractures in prolonged bisphosphonates therapy. The osteonecrosis of the jaw is another side effect in treatment with bisphosphonates drugs. In order to reduce the risk of developing osteonecrosis of the jaw, European Medicines Agency recommended the need to: highlight any dental problems before starting therapy, oral healthcare during treatment; inform the doctors(dentists,GP's) about the treatment with bisphosphonates and contact the doctors if problems with the mouth or teeth occur during therapy. Currently do not exist effective treatments for the osteonecrosis of the jaw. Preventive measures are important and include: oral hygiene, dental examination, management of dental cavities and periodontal disease, avoiding dental implant placement before starting bisphosphonates treatment. The recommended treatment by American Association of Oral and Maxillofacial Surgeons (AAOMS) is individualized according to the stage of evolution of the disease and includes: local antibacterial therapy, treatment with antibiotics, superficial debridement to relieve soft tissue irritation, surgical debridement and or resection.

Key words: osteoporosis, bisphosphonate therapy, osteonecrosis.

INTRODUCTION

Osteoporosis is a condition with a major impact on health. According the WHO criteria, osteoporosis is defined as a BMD that lies 2.5 SD or more below the average value for young healthy women. Dual-energy X-ray absorptiometry (DXA) is the most validated technique for determination of BMD[1].

The morbidity of osteoporosis is secondary to the fractures that may occur. According to WHO "*Common sites of fracture include the spine, hip, forearm and proximal humerus. Fractures at the hip incur the greatest morbidity and mortality, and give rise to the highest direct costs for health services. Osteoporotic fractures at other sites are generally of less economic significance, but they also give rise to significant morbidity and, in some instances, to increased mortality. They occur more commonly than hip fractures at younger ages, and their neglect in evaluating assessment strategies disadvantages the younger segment of the osteoporotic population. The remaining lifetime probability of osteoporotic fractures in women at the age of 50 years exceeds 40% in developed countries. For hip fracture alone, the remaining lifetime probability at the age of 50 years exceeds 20% in women in these countries. In many regions of the world, the risks in men are about half those of women. The number of osteoporotic fractures is certain to increase in both men and women (by more than 3-fold over the next 50 years) as a result of the ageing population*"[1].

The United States Preventive Services Task Force (USPSTF) recommends in 2011 "*screening for osteoporosis in women aged 65 years or older and in younger women whose fracture risk is equal to or greater than that of a 65-year-old white*

woman who has no additional risk factors. The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of screening for osteoporosis in men"[2].

In 2010, the North American Menopause Society suggested to test for osteporosis all women "*age 50 and older with one or more risk factors, including >2 alcoholic drinks per day, rheumatoid arthritis, current smoker, history of hip fracture in a parent, thin with body mass index <21 kg/m^2, or fracture after menopause*"[3].

GENERAL CONSIDERATIONS

Non pharmacological treatment of osteoporosis includes: regular exercise, adequate intake of vitamin D and calcium, avoidance of excess alcohol and quitting smoking.

Bisphosphonates tratment are considered primary therapy in current treatment of osteoporosis. Numerous meta-analysis have high-lighted the efficacy of tratment with bisphosphonates in suppressing bone resorption, increasing BMD and reducing fracture risk in patients with osteoporosis[4, 5]. Current bisphosphonates (alendronate, risedronate, ibandronate, pamidronate, zoledronate) inhibit bone resorption by reducing osteoclastic recruitment, differentiation and mediating induction of osteoclast apoptosis[6].

Studies have highlighted that the oral bisphosphonates, (risendronic and alendronic acid) have been reduced the number of hip and vertebral fractures. Ibandronic acid available in oral and intravenous preparations, reduce only the risk of vertebral fracture[7].

Systematic studies or reviews reported a possible link between atypical fractures and prolonged bisphosphonates therapy[8, 9]. In 2010, Giusti A, Hamdy NA, Papapoulos SE published in Bone a systematic review in which evaluated 32 case series and reported 141 atypical femur fractures. The authors mentioned that *"The results of this analysis allow identification of patients on bisphosphonate treatment at risk of developing atypical fractures, define fractures better as predominantly insufficiency fractures, illustrate that long-term bisphosphonate treatment is not a prerequisite for their development, recognize the use of glucocorticoids and proton pump inhibitors as important risk factors, but do not provide insights in the pathogenesis of these fractures and raise questions that need to be addressed in properly designed studies*"[9]. In a review published in 2011 in Therapeutic Advances in Musculoskeletal Disease entitled "Atypical femur fractures: a review of the evidence and its implication to clinical practice" Girgis CM and Sebel MJ said that "*The predominant hypothesis regarding the pathophysiology of atypical femur fracture is that severe suppression of bone turnover leads to the accumulation of bone microdamage and the development of an insufficiency fracture at the point of maximal, weight-bearing stress, namely at the subtrochanteric or diaphyseal femur*"[10].

Based on the published cases of atypical fractures the Food and Drug Administration (FDA), in June 2008, requested information from oral and injectable bisphosphonates regarding this potential safety. In 2009 an article published in Bone and Mineral Research entitled "Subtrochanteric and diaphyseal femur fractures in patients treated with alendronate: a register-based national cohort study", the authors analyzed data from two large observational studies in patients with osteoporosis and concluded "*that atypical subtrochanteric femur fractures had many similar features in common with classical osteoporotic hip fractures, including patient age, gender, and trauma mechanism. The data showed that patients taking bisphosphonates and those not taking bisphosphonates had similar numbers of atypical subtrochanteric femur fractures relative to classical osteoporotic hip fractures*".

Regarding the optimal duration of bisphos-phonates therapy for osteoporosis the FDA said that "*the optimal duration of bisphosphonates treatment for osteoporosis is unknown – an uncertainty the agency is highlighting because these fractures may be related to use of bisphosphonates for longer than five years*"[12].

ORAL CAVITY IMPLICATIOS OF TREATMENT WITH BISPHOSPHONATES

The osteonecrosis of the jaw is another side effect mentioned in treatment with bisphosphonate drug. The incidence of osteonecrosis of the jaw is estimated by Khosla S *et al* in a review published in 2007 in Journal of Bone and Mineral Research between 1 in 10.000 and <1 in 100.000 patient-treatment years. The risk of jaw osteonecrosis in patients with neoplasm treated with high doses of intravenous bisphosphonates is in the range of 1–10 per 100 patients, depending on duration of

therapy[13]. The simptoms and signs of osteonecrosis include according Ficcara G and Beninat F "*changes in the health of periodontal tissues, non-healing mucosal ulcers, loose teeth and unexplained soft-tissue infection*"[14]. To distinguish osteo-necrosis of the jaw from other affections, the AAOMS has adopted the following definition. Patients may be considered to have osteonecrosis of the jaw if the following characteristics are present:

- previously or currently treatment with bisphosphonates;
- presence of necrotic bone of maxillary and mandibular region that persists for more than 8 weeks; in conditions of absence of radiation treatment to the jaw bones[14, 15].

The pathophysiology for the osteonecrosis of the jaw is associated with the profound inhibition of osteoclast function and bone remodeling. Treatment with bisphosphonates inhibits endothelial cell function and has antiangiogenic properties[15].

After a 2003 caution regarding the possible association between bisphosphonates therapy and osteonecrosis of the jaws, numerous studies and reviews have evaluated this association[16].

In 2005 Marx RE *et al.* analysed the prevalence of dental comorbidities in 119 total cases of bisphosphonate-related bone exposure. 52.1% from patients were treated for multiple myeloma, 42% for metastatic breast cancer, 4% for metastatic prostate cancer and 2.5% for osteoporosis. The authors mention that "*Dental comorbidities included the presence of periodontitis 84%, dental caries 28.6%, abscessed teeth 13.4% root canal treatments 10.9%, and the presence of mandibular tori 9.2%. The precipitating event that produced the bone exposures were spontaneous 25.2%, tooth removals 37.8%, advanced periodontitis 28.6%, periodontal surgery 11.2%, dental implants 3.4% and root canal surgery 0.8%*"[17].

In the same year Bamias A *et al.* published in Journal of Clinical Oncology one study in which evaluated the incidence and risk factors for the development of dental comorbidities among patients treated with bisphosphonates for bone metastases. In the study were included 252 patients who received bisphosphonates between January 1997 and July 2003.

17 patients (6.7%) who participated in the retrospective study, developed osteonecrosis of the jaw (11 patients with multiple myeloma, 2 with breast cancer, 3 with prostate cancer, and one with other neoplasms. The authors pointed out that the incidence of osteonecrosis of the jaws increased with time to exposure from 1.5% in case of treatment under 1 year to 7.7% for treatment of 37 to 48 months[18].

A reviewe by Woo *et al.* published in 2006 in Annals of Internal Medicine entitled "Narrative [corrected] review: bisphosphonates and osteonecrosis of the jaws" the authors mention that "*The mandible is more commonly affected than the maxilla (2:1 ratio), and 60% of cases are preceded by a dental surgical procedure. Oversuppression of bone turnover is probably the primary mechanism for the development of this condition, although there may be contributing comorbid factors. All sites of potential jaw infection should be eliminated before bisphosphonate therapy is initiated in these patients to reduce the necessity of subsequent dentoalveolar surgery. Conservative débridement of necrotic bone, pain control, infection management, use of antimicrobial oral*"[19].

In 2012, Diniz-Freitas M. *et al.* have published the result of a retrospective multicentre study. The authors analyzed the medical records of all patients who had been diagnosed with osteonecrosis of the jaws related to the use of oral bisphosphonates (alendronate 16 patients and ibrandronate 4 patients) during the period from May 2008 through April 2011. The conclusions of the study were as the osteonecrosis of the jaws induced by oral bisphosphonates "*typically develops in women around 70 years of age, taking alendronate for 4.5 year that underwent oral surgery in the 12 months prior. Although specific risk factors have been described, they are not detected in all patients, which lead us to speculate that there may be other, as yet unidentified risk factors*"[20].

In 2015, the European Medicines Agency's Pharmacovigilance Risk Assessment Committee has completed a periodic review abot the known risk of osteonecrosis of the jaw related to the use of bisphosphonates. The card recommended by agency mentioned above will remind patients about:

- the benefits and risks of bisphosphonates therapy;
- the possble risk of osteonecrosis of the jaw during treatment with bisphosphonates and the necessary measures, respectively: the need to highlight any dental problems before starting treatment; ensure oral healthcare during therapy and to inform the dentist of therapy with bisphosphonate and to contact the doctors if problems with oro dental pathology apear during treatment[21].

MANAGEMENT OF ORAL CAVITY COMORBIDITIES IN PATIENTS TREATED WITH BISPHOSPHONATES

Preventive measures recommended by specialists in the field include: oral healthcare, dental examination, management of dental caries and periodontal disease, dental treatment (including extractions), avoiding dental implant placement before of the start of bisphosphonate treatment[15, 22, 23].

Currently do not exist effective treatments for the osteonecrosis of the jaw. AAOMS has developed the treatment strategy for patients with this condition.

The American Association underlines three stages of the evolution of the condition: stage 1 of the condition is characterized by the absence of symptoms, stage 2 by "*exposed/necrotic bone associated with infection, presence of pain and erythema in the lesional area with or without purulent drainage*" and stage 3 by "*exposed/necrotic bone in patients with infection and pain, presence of one or more of the following: extraoral fistula, osteolysis extending to the inferior border, pathologic fractures*". Patients in stage 1 require local antibacterial therapy, clinical follow-up every 4 months. For stage 2, AAOMS recommend local antibacterial therapy, treatment with antibiotics, management of the pain and superficial debridement to relieve soft tissue irritation. Patients in stage 3 require local antibacterial therapy, antibiotic treatment, management of the pain and surgical debridement and or resection[15, 16].

CONCLUSIONS

Studies have shown the benefits of bisphosphonates in treatment of osteoporosis. The prolonged bisphosphonate therapy is accompanied by a number of adverse effects, respectively atypical fractures and osteonecrosis of the jaw. In order to minimize the risk of developing osteonecrosis of the jaw, European Medicines Agency recommended the need to: highlight any dental problems before starting treatment; ensure oral healthcare during therapy and to inform the dentist of therapy with bisphosphonate and to contact the doctors if oro dental complications occur during treatment. Preventive measures are important in diminishing the risk of this complication and include: oral hygiene, dental examination, control of periodontal disease and caries, avoiding dental implant placement before starting the bisphosphonate treatment. The recommended treatment by AAOMS is individualized according to the stage of evolution of the disease and includes: local antibacterial therapy, treatment with antibiotics, management of the pain, superficial debridement to relieve soft tissue irritation, surgical debridement and or resection.

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