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Retrospective study regarding the appearance of osteonecrosis related to bisphosphonate therapy

ADELA CRISTINA LAZĂR[1)], ROXANA SOCACIU[2)], OVIDIU MUREŞAN[3)], MARIANA PĂCURAR[4)]

[1)]*Department of Oral Rehabilitation, Oral Health and Dental Office Management, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania*

[2)]*Postgraduate Student, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania*

[3)]*Department of Oral and Maxillofacial Surgery, "Iuliu Haţieganu" University of Medicine and Pharmacy, Cluj-Napoca, Romania*

[4)]*Department of Orthodontics, "George Emil Palade" University of Medicine, Pharmacy, Science, and Technology of Târgu Mureş, Romania*

Abstract

Bisphosphonates are analogues of the natural compound pyrophosphate and one consequence of the mechanism of action of bisphosphonates on bone metabolism is the reduction of bone turnover, replenish the resorption spaces and to mineralize the extracellular matrix. Osteonecrosis of the jaw is the most common side effect of bisphosphonates and most often occurs after an invasive dental procedure, such as dental extraction. The existence of a maxillary bone infection leads to a delayed healing reaction manifested by the presence of areas necrotic bone, exposed in the oral cavity, which persists for more than eight weeks and has no tendency to heal. In most cases, the dentist is the first one who can detect the onset of osteonecrosis even in the early stages, thus being able to direct the patient to a hospital unit where he/she receives the treatment of necessity. The aim of this retrospective study is to determine the link between bisphosphonate therapy and the occurrence of necrosis of maxillary and mandibular bone. This study was conducted on 22 patients hospitalized for different stages of bone necrosis for a period of two years. The prevalence of osteonecrosis is higher in menopausal women and also after a certain period after the bisphosphonate therapy is closed.

***Keywords*:** bisphosphonates, osteonecrosis of the jaw, dental procedures, menopause.

Introduction

Bone tissue is a living tissue, which is in a process of continuous modeling, in relation to the growth and development of the skeleton. The bone remodeling process has a few main goals [1]: regulation of the content of the essential minerals by changing their concentration in the blood; maintaining bone strength during repetitive cycles of mechanical stress by repairing the damage that occurred during these cycles, and preventing excessive deterioration due to age; providing growth factors to the bone marrow; adaptation of the skeleton to the mechanical environment, reducing the risk of fracture.

Bisphosphonates are analogues of the natural compound pyrophosphate, which has the basic structure type P–O–P, which is fixed at the level of calcium phosphate crystals; bisphosphonates have affinity for calcium phosphate crystals in the apatite structure. Their adherence to bone surfaces provides their specific action at the bone level [2]. Bisphosphonates have the main effect of marked reduction of bone resorption. The markers of bone resorption decrease rapidly, reaching the minimum value at 6–12 weeks. Bone formation remains unaffected initially, and subsequently decreases, resulting in the overall reduction of bone turnover [2]. What sets bisphosphonates apart from other anti-catabolic drugs is their most significant effect of reducing bone remodeling [3].

One consequence of the mechanism of action of bisphosphonates on bone metabolism is that the reduction of bone turnover provides the time needed to replenish the resorption spaces and to mineralize the extracellular matrix, which has consequences on increasing bone mineral density [4].

Bisphosphonate therapy has a maximum effect on bone mass in the first year of administration, after which the gain of bone mineral density gradually decreases [2]. Bisphosphonate therapy can be given in the case of osteoporosis, bone metastases, Paget's disease, presenting a series of benefits to the patient's life, by stopping the evolution of localized or generalized bone degradation [5]. Bisphosphonates are given orally or in injection form. Biological effects are ensured in both forms of administration because the entire amount absorbed is taken up by hydroxyapatite binding and concentration in bone resorption areas. The rest of the administered amount is excreted without metabolic changes in the kidney [1].

Osteonecrosis of the maxillary bones is a common adverse effect of bisphosphonates therapy, regardless of the type of bisphosphonate administered. It is defined as avascular necrosis of the maxillary bones in patients who have undergone or are receiving bisphosphonate treatment, which is largely due to osteoclast activity [6]. Thus, there is a disturbance of the physiological process of resorption, which results in an inhibition, thus resulting in a non-vital bone on important surfaces. The absence of bone proteins and cytokines decreases the attachment of new minerals, leading to a microfracturable bone in the bone matrix with large areas of nonvital osteoclasts [7]. The existence of a maxillary bone infection leads to

a delayed healing reaction manifested by the presence of necrotic bone areas, exposed in the oral cavity, which persists for more than eight weeks and has no tendency to heal.

Osteonecrosis of the jaw (ONJ) associated with bisphosphonates therapy was identified as a pathological entity in 2004 by Ruggiero. In order to establish the diagnosis of ONJ associated with bisphosphonate treatment, the *American Association of Oral and Maxillofacial Surgeons* (AAOMS) establishes three diagnostic criteria: current or previous treatment with bisphosphonates; denuded, necrotic bone at the level of the maxilla or mandible, which has persisted for over eight weeks; absence of ionizing radiation treatment in the region of the jaws.

Osteonecrosis occurs with a frequency of 30% in the maxilla, 60% in the jaw and 10% in both [8]. ONJ most often occurs after an invasive dental procedure, such as dental extraction. ONJ may also occur in patients undergoing radiation therapy to the head and neck (radiation-induced osteonecrosis), in patients with viral infections (herpes zoster), in osteomyelitis, as well as in patients on corticosteroid therapy [9]. Clinically, ONJ is shown to be an exposed bone area, hypodynamic with decreased biomechanical skills, hypocellularity and radiologically observed bone lysis, with delayed healing or without healing over a period of 6–9 weeks [10]. In 80% of the cases, the lesions have a burning character and in 69% of the cases, they occur after dental surgery [11].

Aim

The aim of this study is to determine the link between bisphosphonate therapy and the occurrence of osteonecrosis of maxillary and mandibular bone in the context of surgical dental procedures.

Patients, Materials and Methods

This retrospective study was performed at the Ist Clinic of Oral and Maxillofacial Surgery, Cluj-Napoca, Romania, between September 2017–May 2019. The total number of patients enrolled in the study was 22, divided into groups of males and females. They were hospitalized within the department for specialized treatment in the context of the occurrence of osteonecrosis of the maxillary bones associated with the chronic bisphosphonate therapy. All patients have signed the informed consent regarding the protection of personal data, according with General Data Protection Regulation (GDPR).

The inclusion criteria of the subjects were the following: chronic treatment with bisphosphonates; the presence of necrosis of the maxillary bones; patients who showed up only for a certain period of time (September 2017–May 2019).

Subject exclusion criteria: patients with other diagnoses than osteonecrosis associated with bisphosphonate therapy.

For each patient, a series of parameters were followed, which were introduced in this clinical study: age; gender (female/male); environment of origin (urban/rural); the type of bisphosphonate administered (Zometa®, Fosamax®, Actonel®, Boniva®); continuity of bisphosphonate therapy at present; the time of occurrence of osteonecrosis of the maxillary bones (during bisphosphonate therapy/after closure of bisphosphonate therapy); inpatient diagnosis; the basic condition for which bisphosphonates were administered; secondary pathology associated with the basic disease; risk factors for osteonecrosis associated.

Statistical analysis was performed with the Microsoft software package. The processing was performed with the help of Cross, Basic Tables, correlation, regression, Factor Analysis and Data Analysis module of the Excel package. The main statistical indicators used in the paper were arithmetic mean and standard deviation. For the demonstration of the statistical differences, we used Analysis of Variance (ANOVA) test and Quark Square test.

Results

From the number of 22 patients who participated in the study, seven were males, representing 32% of the total, and the remaining 15 were females, representing 68% of the total patients. We wanted to make a first classification according to gender, because we wanted to emphasize the prevalence of bisphosphonate treatment especially in women, in the context of osteoporosis. Therefore, as seen in Figure 1, the highest prevalence of osteonecrosis associated with bisphosphonate treatment is at women, compared to men, who develop this side effect of bisphosphonates more rarely.

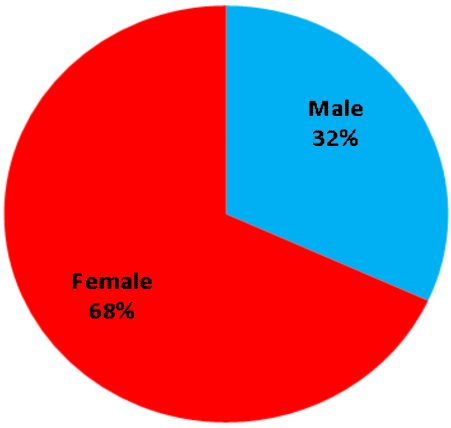

Figure 1 – ***Gender distribution of the patients.***

The bone is a living, dynamic tissue, constantly changing. In order for the bones to remain strong throughout life, our body removes the old bone and replaces it with a new one. Childhood and adolescence are the essential periods when our bone mass is formed: the bones grow, become longer and stronger, and this rhythm continues until 25–30 years old, when the maximum bone mass is reached. After this age, the bones undergo a continuous process of formation and destruction that allows them to stay healthy. However, when women turn 40 or 50 years old, this balance changes, because it is no longer possible to replace bone tissue as soon as it is removed. And this effect is even more pronounced in women in the first years after menopause, when the protective effect of the estrogen hormone is lost. According to our study, women between 50–60 years old (Figure 2) who undergo menopause and currently take or have taken in the past months or years bisphosphonate therapy, have a higher rate of increasing osteonecrosis due to this treatment.

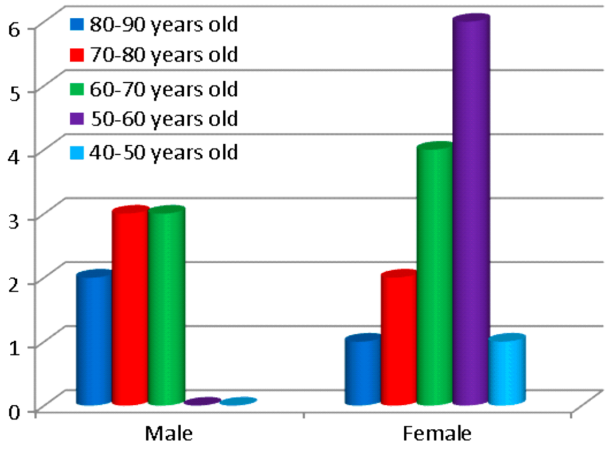

Figure 2 – ***Patients distributions by age and gender.***

Due to the generous pharmaceutical supply of bisphosphonate preparations, a diagram was drawn which shows that the most used preparation is Zometa®, being administered to 12 of the 22 patients, in order to prevent bone metastases. Following it is the Fosamax® preparation, which is administered to four patients (Figure 3).

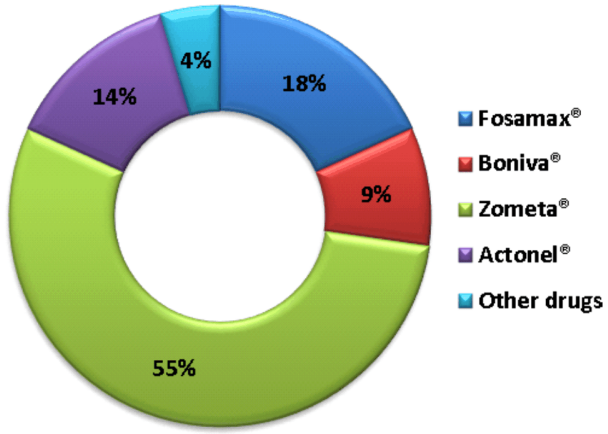

Figure 3 – ***The most common used bisphosphonates regarding the commercial name.***

Intravenous administration of bisphosphonates, such as Zometa®, increases the risk of osteonecrosis. At the same time, the duration of bisphosphonate treatment has important repercussions on the appearance of osteonecrosis. Out of the total number of 22 patients (Figure 4), the majority (19 patients) developed maxillary osteonecrosis after treatment with bisphosphonates, while only three patients developed bisphosphonate-related osteonecrosis of the jaw (BRONJ) during bisphosphonate therapy.

Discussions

Bisphosphonates are antiresorptive agents used in the treatment of osteoporosis, multiple myeloma, Paget's disease and solid metastatic tumors [12]. Bisphosphonates enter the osteoclasts through endocytosis and inhibit their activity [13]. Despite their beneficial effects in the prevention of osteoporotic fractures and in the prevention of side effects from bone cancer, in the United Kingdom there has been a sharp decline in bisphosphonate prescriptions in the last few years, more precisely from 21.3 million in 2002 to 14.7 million in 2012, significantly increasing the ratio of side effects of bisphosphonates [14].

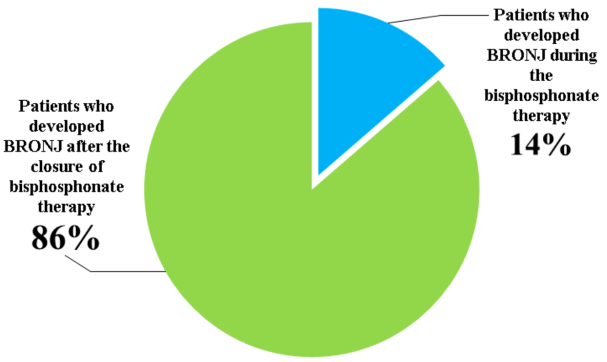

Figure 4 – ***Distribution of patients according to the time of occurrence of bisphosphonate-related osteonecrosis of the jaw (BRONJ).***

Age has a close correlation in the development of osteonecrosis, due to the physiological effects of aging, including inflammatory changes, immune dysfunction, reduced blood circulation, and bone remodeling [15]. In our study, female patients' age between 50–60 years old is more prone to develop ONJ rather than other categories and also rather than male with same age.

All drugs used to treat osteoporosis interfere with bone metabolism. The mechanism of action of these two categories of drugs is different with respect to bone remodeling and fracture prevention [16, 17]. In our study, most of the patients were given bisphosphonate with commercial name Zometa® (55%), followed by Fosamax® (18%) for different pathologies like osteoporosis and prostate carcinoma. Depending on the intensity of the given effect, the class of anti-catabolic drugs is further divided into two categories: weak (Calcitonin, Vitamin D and Calcium, Raloxifene), strong (bisphosphonates, estrogen hormones). Their major principle of action is the global reduction of bone turnover [18]. Anti-catabolic drugs do not have the ability to perform the following actions, absolutely necessary in the treatment of osteoporosis [1]: improvement or maintenance of bone formation, stimulation of cortical thickening, restoring the trabecular microarchitecture. Unlike anti-catabolic drugs, which lower bone turnover, anabolic ones initially increase it.

Bone metastases frequently occur in the evolution of malignancies, with a significant morbidity, which leads to bone pain, pathological fractures, hypercalcemia and neurological compression, which may ultimately lead to loss of mobility or even autonomy [19]. Bisphosphonates are used because they have the ability to withstand the osteolytic process secondary to osteoclast hyperactivity. Intraosseous tumor cells secrete humoral mediators, such as cytokines. These mediators activate osteoclasts and thus increase bone resorption. Thus, on the one hand, a series of symptoms due to bone fragility result, and on the other, a local release of the growth factors of the matrix that stimulate the proliferation of tumor cells, thus maintaining a vicious circle. Treatment with bisphosphonates has a strong action to inhibit the action of osteoclasts and therefore decrease bone resorption. Some more recent data suggest that certain types of bisphosphonates may have direct antitumor action on tumor plasma cells, mammary and prostate tumor cells, inducing apoptosis. The efficacy

of bisphosphonates has been demonstrated in the management of bone fragility symptoms during malignant osteolysis [20–22].

Osteonecrosis of the maxillary bones is one of the most known and serious side effects, being characterized by necrosis of the maxillary bones and necrotic bone exposed by mucous membrane or skin tissue [23–25]. In our study, 86% of the patients developed different stages of ONJ after the closure of bisphosphonate therapy. Surgery and gingival infections are known to be direct causes of osteoporosis of the jaws, but the main mechanism of occurrence has not yet been fully elucidated [26]. Considering the prevalence of the installation only in certain patients, multiple studies have been performed to confirm the genetic component underlying the installation of this condition [26–28]. The risk of developing osteonecrosis of the maxillary bones after bisphosphonate administration in osteoporotic patients is lower than in oncological patients receiving bisphosphonate therapy [20].

Following studies that have been conducted with Clodronate at conventional doses of 1600 mg, it has been observed that its efficacy is lower in patients with myeloma, than in patients with metastatic breast carcinoma, where it was more effective [21]. In a study that followed patients with bone marrow micrometastases, the oral use of Clodronate significantly reduced the occurrence of bone metastases and even soft tissue metastases, thus increasing survival [22].

Conclusions

Necrosis of the maxillary bones is a common disorder in the maxillofacial area, being most often the consequence of bisphosphonate treatment. It is prevalent in menopausal women diagnosed with osteoporosis and develops this bone disease at a certain time after bisphosphonate therapy is completed. In most cases, the dentist is the first one who can detect the onset of osteonecrosis even in the early stages, thus being able to direct the patient to a hospital unit where he/she receives the treatment of necessity. Despite the appearance of new generations of bisphosphonates, they continue to cause necrosis of the maxillary bones as a side effect. Thus, new studies are coming to identify the negative potential of bisphosphonates and how this can be stopped in the long term.

Conflict of interests

The authors declare that they have no conflict of interests.

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Corresponding author
Adela Cristina Lazăr, Assistant Professor, DMD, PhD, Department of Oral Rehabilitation, Oral Health and Dental Office Management, "Iuliu Haţieganu" University of Medicine and Pharmacy, 15 Victor Babeş Street, 400012 Cluj-Napoca, Romania; Phone +40748–290 425, e-mail: lazar_adela@yahoo.ro

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