

BISPHOSPHONATE-RELATED OSTEONECROSIS OF THE JAWS

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Introduction.

Osteonecrosis of jaws induced by the use of bisphosphonates (BRONJ) is described as a pathological entity in 2003 by Marx in the United States of America. Osteonecrosis of the jaws occurs as a consequence of the side effects of bisphosphonates, being a relatively rare complication of the jaws. This pathology meets three criteria: painful necrotic areas exposed in the oral cavity, patients who have not undergone radiotherapy on head-to-neck segments, and necrotic areas persist for over eight weeks without signs of healing. In recent years (2001-2017), there is an increase in BRONJ although the pathogenesis of osteonecrosis of the jaws associated with BPs is not fully elucidated, but it is known that BPs alter bone angiogenesis and microarchitecture.

Aim. In this paper we propose to evaluate the main aspects of the mechanisms of action of BPs, the risks and benefits of BPs, and the treatment methods used at various stages of BRONJ that must be known by both oncologists, endocrinologists, hematologists (those who prescribe drugs) as well as by dentists or maxillofacial surgeons (to whom patients are ultimately addressed due to the localization of jaw pathology). We also proposed to reproduce a rat model with this pathology to serve further studies and to evaluate the dentist's knowledge about this pathology.

Material and method.

In the first we conducted a questionnaire survey amongst dentists in Targu Mures in October and November 2014. 40 questionnaires were handed to practitioners at local meetings and courses at the Faculty of Dental Medicine Târgu Mureş and other questionnaires were sent to e-mail and social networks. The questionnaire included a total of 13 questions, and practitioners who were asked to fill out the questionnaires were dentists, residents and specialists in the dental medicine branches. They were asked to choose one or more of the options offered.

The second study is an experimental study on rats. Thirty-six (36) rats were randomly assigned to three groups of twelve (12) animals each. A surgical flaw at the palate was performed seven days after the last administration of the group-specific drugs, namely: group one - subcutaneous administration of zoledronic acid (ZA) and dexamethasone (DX), group two - ZA and group three - saline solution. Local surgical defects were performed in the palatal area near the maxillary molars on the right hemiarcade. Fourteen days after the bone defect, we euthanated the animals and collected samples for histological analysis.

In the third study, conducted in June 2018, we intended to use the same questionnaire and compare the dental practitioner's knowledge over these four years about the treatment they can use in dental surgeries in patients currently or in the past with BPs. We also intend to observe the addressability of patients who undergo BP therapy during 2013-2018 at the Oro-Maxillofacial Surgery Clinic in Cluj-Napoca for the necessity of surgical treatments.

Results.

In the first study, 70 questionnaires were returned. During the medical history most clinicians (60%) asks if follow/ followed treatment with bisphosphonates, most of them (42.85%) did not perform treatments in these patients, 85.71% of respondents say they do contact the prescriber before performing surgical treatment, and 48,57% do not know under what conditions can they perform treatment.

In the second study, the macroscopic results in group 1 revealed open wounds noted in the majority of subjects, only 5 showed exposed bone. In group 2 open wounds and exposed bone were observed in the majority of all eight rats remained in the experiment, and in group number 3 all subjects proved a real healing. For the microscopic results, HE staining was performed to help determine the condition of osteoblasts, osteoclasts, the presence of exposed bone, inflammatory cell infiltrate and vascularity. In control group, the results in sections showed that the rats developed normal healing of bone, almost entirely healed epithelium. In group 1, Za+ Dx, specimens demonstrated qualitative differences from controls related to the integrity of overlying mucosa, a number of bony sequestra, the extent of bone cellularity. Although focal necrosis was present in many animals treated with ZA and DX, was observed the presence of extensive osteocartilaginous regeneration through chondrocyte hyperplasia in place of bone tissue In group 2, ZA, in most samples, we could see the appearance of a dense fibrous connective tissue at the level of the created bone defect. Many empty bone lacunae, marginal bone loss, a lot of necrotic bones infiltrated with inflammatory cells.

In the third study, 120 questionnaires were returned. The majority (n=113, 94.2%) included in their medical records the question regarding the use of BPs. Of all respondents, 48 of them (40%) perform dental or surgical treatment on patients undergoing BP therapy, 68 (56.7%) did not perform, and four of the respondents (3.3%) did not know. At the last question, 100 (83.3%) respondents always contact the prescriber prior to surgery in these patients, regardless of how BPs are administered. In the second part of the third study, 76 patients were internalize to the Oro Maxillofacial Surgery Clinic in Cluj-Napoca between 2013 and 2018. The criteria for inclusion were the patients with the diagnosis of osteonecrosis in the jaw or osteomyelitis and who were following treatment with BPs.

Conclusions.

1. We believe that dentists are not well informed about this pathological entity known only since 2003 and that in the absence of appropriate protocols can not provide a quality treatment and in these circumstances they may do more harm than good.
2. The strengths of the second study is that we achieved a BRONJ model with a high dose of medications than in humans in a short time. With our model we expect to provide useful informations for further studies in the research of this severe disease. However, the present study was limited, because it was performed on a rat model, which has different anatomy and bone turnover and structure compared to humans.
3. According to the findings of the third study, many of the respondent doctors had heard about the BPs and it's complications, but they do not know the fundamental concepts for the prevention of BRONJ and treatment protocols. Despite the small size of the sample studied, the data are sufficient to say that BRONJ's dentist knowledge and treatment of patients undergoing BP therapy have improved over the last four years.