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Osteonecrosis of the jaw as a serious adverse effect of bisphosphonate therapy and its indistinct etiopathogenesis

Osteonekroza vilica kao ozbiljan neželjeni efekat terapije bisfosfonatima i njegova nejasna etiopatogeneza

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Introduction

Bisphosphonates (BPs) represent a class of drugs that are applied in therapy of different pathological conditions related to bone. Their main role in bone metabolism is to inhibit osteoclast function, so these drugs act as potent devices in suppression of the bone resorption process. Considering the presence of two phosphonate groups with a high affinity for calcium ions in their chemical structure, BPs have the ability to accumulate predominantly in bones [1]. According to the differences in side chain, related to the presence or absence of nitrogen atom, BPs are classified in two different groups: nitrogen containing (aminoBPs) and non-nitrogen containing (non-aminoBPs) drugs. These two groups of bisphosphonates also differ in mechanism by which they inhibit osteoclast action. Aminobisphosphonates (pammidronate, neridronate, olpadronate, ibandronate, risedronate, zoledonate) act directly on HMG-CoA reductase (mevalonate) pathway by binding and blocking enzyme farnesil diphosphate synthetase (FPPS) [2]. Non-amino bisphosphonates (etidronate, clodronate, tiludronate) are metabolised within osteoclasts to analogues of adenosine triphosphate (ATP) that accumulate within the cells, which leads to inhibition of numerous metabolic enzymes, cytotoxicity and apoptosis [3–6]. Nitrogen addition greatly increases the potency of bisphosphonate, so aminoBPs are claimed to be 10–10,000 times more potent comparing non-aminoBPs [7].

As they act as inhibitors of osteoclast function in order to suppress bone resorption and improve bone mineral density, during the past three decades, bisphosphonates have been increasingly used in therapy of diferrent pathologic conditions related to bone. Intravenous BPs are principally used for treatment of metastatic bone lesions, multiple myeloma and hypercalcemia of malignancy. Oral BPs take part in therapy of osteoporosis, Paget disease and paediatric osteogenesis imperfecta. Positive effects of bisphosphonates in these conditions are: significant reduction of bone pain, osteolytic lesions and fracture risk, and improvement of bone mineral density.

BPs are considered as drugs of certified efficiency, with rare negative side effects, such as gastrointestinal intolerance, headache, hypocalcemia, hypophosphatemia, bone pain, dizziness, fever, fatigue etc. [8], probably due to their low serum concentration and rapid accumulation in bone matrix.

History and definition of bisphosphonate-related osteonecrosis of the jaw

In 2003 Marx [9] described non-healing and painful exposure of jaw bone after intravenous administration of potent aminobisphosphonates in patients with multiple myeloma and metastatic bone lesions, and soon, this adverse effect was named bisphosphonate-related osteonecrosis of the jaw (BRONJ).

BRONJ in a short time became the main and most speculated adverse effect of BPs therapy [10]. In 2009 the American Association of Oral and Maxillofacial Surgeons (AAOMS) defined criteria for BRONJ: the presence of exposed necrotic bone in maxillofacial region for more than 8

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weeks in patients that currently take, or used to take bisphosphonates, with no history of radiation therapy to the jaws [11]. AAOMS also proposed staging system for BRONJ according to symptoms, clinical and radiographic findings, and recommended treatment strategy for each stage (Table 1) [11]. Risk factors included in developing BRONJ are pointed out in many studies on this subject [3, 11–14]. Now it is known that BRONJ mostly occur in patients who used to receive more potent, nitrogen containing BPs, in the treatment of multiple myeloma or metastatic bone lesions. Long-term therapy and intravenous administration of BPs are associated with increased risk for developing BRONJ. Local risk factors include oral-surgery interventions, such as tooth extraction, implant placement etc., but also chronic irritations (inadequate dentures), and chronic periodontal disease. In the majority of reported cases, local trauma, particularly tooth extraction, appear to be the direct cause, in fact, the trigger factor in developing BRONJ, yet there are reported cases that occur spontaneously, with no previous dental treatement, or trauma [12, 15]. Futhermore, there are also areas within the jaws, that show greater predilection to this complication. Lesions are found more commonly in the mandible than in the maxilla (ratio 2 : 1), and more often in areas where thin oral mucosa overlies bony prominences and ridges [11, 15].

Table 1

Bisphosphonate-related necrosis of the jaw (BRONJ) risk staging

BRONJ stages	Clinical features	Treatment strategy
Patients at risk	No apparent necrotic bone in asymptomatic patients treated with IV or oral bisphosphonate.	Patients should be informed on the risks of developing BRONJ.
Stage 0	No clinical evidence of necrotic bone, but the presence of non-specific symptoms or clinical and radiographic findings that address osteonecrosis.	Symptomatic treatment and conservative management of local factors, such as caries and periodontal disease.
Stage I	Exposed and necrotic bone in asymptomatic patients with no evidence of infection.	Antimicrobial rinses, such as chlorhexidine 0.12%.
Stage II	Exposed and necrotic bone in patients with pain and clinical evidence of infection.	Antimicrobial rinses in combination with antibiotic therapy.
Stage III	Exposed and necrotic bone in patients with pain, infection and one or more of the following: exposed necrotic bone extending beyond the region of alveolar bone; pathologic fracture; extra-oral fistula; oral antral/ oral nasal communication; osteolysis extending to the inferior border of the mandible or sinus floor.	Surgical debridement, including resection in combination with antibiotic therapy.

Incidence of bisphosphonate-related osteonecrosis of the jaw

According to the current literrature review [16] the incidence of BRONJ associated with parenteral administration, showed a high variation from 0.00% to 27.5%, mean value 7% (in studies reported from 2003 to March 2010), but these reviewed studies showed also high variance in duration and design (retrospective, prospective, letters to editor and review).

The overall incidence of BRONJ associated with oral bisphosphonate therapy was estimated to be 0.12%, ranging from 0.00% to 4.3%, also with variations in study type and its duration [16].

The importance of investigation of biphosphonate therapy

While the clinical presentation of BRONJ is well-known and described, the exact etiology and pathogenesis still remains an enigma, despite a number of suggested theories that tried to give an appropriate explanation. Besides, the question that has not been completely answered yet is: Why are the jaws almost the only affected area? There were rare reports in the literature of bisphosphonate-related osteonecrosis affecting other bones [17–21], so jaws remain, certainly the main target for this complication of BPs therapy.

Cognition of the exact etiology and pathogenesis of this adverse effect may make it be predictable, help its prevention and facilitate its treatment, which is often without an adequate response.

Etiopathogenesis

While there is more or less concordance among reports in clinical presentation and risk factors related to BRONJ, a concrete etiology and pathogenesis are still confusing and therefore, there is a tendency in the literature to give an appropriate explanation for this adverse effect of bisphosphonate therapy.

Suggested hypotheses are related to bone turnover suppression, angiogenesis suppression, soft tissue toxicity, infection and local pH value changes, immune system deficiency, and genetic predisposition [22–26].

Via osteoclast inhibition (what is actually their mechanism of action), BPs definitely, on many levels, disturb communication and signaling pathways among cells included in bone remodelling, which leads to supression of this process or at least to its defective enactment. As jaws have a high remodelling rate, they would be the most affected area [27]. Whereas the osteoclasts are, undoubtly, the main target cells for BPs, there are also speculations and studies about BPs' effect on other bone cells: osteocytes and osteoblasts, which affection could play a role in pathogenesis of BRONJ, too.

BPs cause acumullation of avital bone matrix with non-viable osteocytes, which has been already proved on animal model [28], but it has not been clarified yet whether it is a consequence of their indirect action, through remodelling supression, or direct effect on osteocytes' viability, when these cells are exposed to high concentrations of BPs.

In *in vitro* studies of BPs' action, the direct effect of BPs on cells of the osteoblast lineage is confirmed and appeared to be dose-dependent, so it seems that BPs may inhibit bone formation process, too [29, 30].

Subramanian et al. [31] actually believe that combined reduction in bone formation and bone resorption leads to signifficant attenuation of bone remodelling response to physiological stimuli such as bone aging, microdamage and mechanical stress, so bone matrix with apoptotic osteocytes persists unresorbed and unrepaired. Finally, BRONJ develops when local remodelling aparature is not able anymore to maintain homeostasis and respond to bone damage subsequent to dentoalveolar infection, local trauma, or , the most frequent, tooth extraction.

The effect of BPs treatement on vasculature has been speculated in some studies [22, 23]. It is familiar that BPs act as potent devices in suppression of angiogenesis associated with tumor growth, and their antiangiogenic effect has been documented. Exposed bone subsequent to BPs therapy does not bleed and it is visiably avascular. However, more potent substances with antiangiogenic action, that are in clinical use, do not lead to osteonecrosis of the jaw, except reported cases of treatement with bevacizumb- monoclonal human antibody that through inhibition of vacular endothelial growth factor A (VEGF-A) achieves antiangiogenic potential [32]. Since these reports are extremly rare, we cannot make a conclusion of antiangiogenic effect of BPs as the main causal factor included in etiopathogenesis of BRONJ. In 2010, Yin, Bai and Luo [22] established a hypothesis of addititious, indirect antiangiogenic effect of BPs, *via* inhibition of osteoclasts, that impact this process, and further suppression of angiogenesis as in the study of Cackowski et al. [33].

Furhermore, it has been suggested that BPs accumulated in bone after tooth extraction play with direct toxic effect on oral epithelium, keratinocytes and fibroblasts, compromiting soft tissue healing, so the exposed bone becomes necrotic [25, 34, 35]. Otherwise, reported cases of BRONJ that develops without prior invasive intervention, such as tooth extraction, confront this theory. Besides, an open question is whether or not oral mucosa is exposed to enough concentrations of BPs, which are known to accumulate, predominantly, in bone?

Otto et al. [24, 35] hypothesized that local infection and subsequent changes of local pH value have important role in pathogenesis of BRONJ. AminoBPs are known to bind to bone matrix in neutral pH, but their relase and activation take place in acid environment, which starts cascade of pathways and leads to BRONJ. Since jaws, especially mandible, are acessible to infecton, despite other area of the skeleton, this theory could give an atrractive explanation of the pact that osteonecrotic process predominanatly affects jaws. This pathophysiological mechanism has been proved *in vitro*, on cellular level, where it has been adjusted that nitrogen containing BPs act as more toxic in acid environment, in contrast to non-nitrogen containing BPs [36]. Having in mind this study, the fact that BRONJ mostly occures in cases with *iv* administration of aminobisphosphonates, might not be surprising. Recent studies pointed at *Atctinomyces* colonisation associated with BRONJ [37] and one metagenomic study revealed *Proteobacteria, Furmicutes* and *Actinobacteria* being the domminant phylotypes in BRONJ patients, but also detected associated viruses [38].

It is still unclear, yet, whether extraction or infection is the real trigger for BRONJ development. This theory, however, related to pH value changes, explains why preventive measures before and during BPs therapy are very important and successful, which has been proved in some studies [39, 40]. Tooth extraction is always associated with loss of integrity of the soft and hard intraoral tissue. This procedure enables direct invasion of intraoral microorganisms into extraction socket. Because of abundance of microorganisms in the oral cavity, also regarding the previous fact, it is difficult to consider extraction without infection.

None of these theories could give a complete, conspicuous explanation for etiopathogenesis of BRONJ. It seems that all these theories are complementary to each other, and the majority of promoted mechanichms could be included in this process, although none of them has been experimentally confirmed.

A relatively new bone antiresorptive agent, denosumab, that is approved by the Food and Drug Administration for use in patients with osteoporosis and metastatic bone disease, has been associaeted wit osteonecrosis of the jaw, too. Nevertheless, according to its different pharmacology characterisics and more rapidly reversible impact on bone turnover comparing to bisphosphonates, as it was explained in a study by Malan et al. [41], osteonecrosis of the jaw related to denosumab might resolve in a shorter drug holiday period.

Treatement strategy and outcome

The treatment strategy for managing BRONJ depends on the stage of this condition (Table 1) and consists of preventive measures, antibiotic medication, surgical debridement/resection and sometimes even discontinuation or modification of bisphosphonate therapy. The last mentioned should be done only if systemic conditions permit and in obligate consultation with the treating physician or oncologist and patient about risks and benefits of continuing bisphosphonate therapy [42].

There is an agreement among all experts about treatment difficulties concerning BRONJ, because of frequent relapse after conservative or surgical therapy. Doubtless, implementation of adequate prevention measures in patients treated with bisphosphonates are very important and require a multidisciplinary approach.

Clinical manifestation of BRONJ could be very similar to many pathological conditions of maxillofacial region. Considering differential diagnosis, it is very important for clinical to get detailed anamnesis from patients (previous

BPs administration, malignancy or osteoporosis). Clinic have to distinguish BRONJ from other lesions in maxillofacial region (oral carcinoma, cysts, chronic irritation of oral mucosa, alveolitis after tooth extraction, malignant ameloblastoma) because the treatment strategies of these pathologies are completely different [43, 44].

Conclusion

It could be concluded that BRONJ is a serious negative side effect of bisphosphonate therapy, that impacts negatively on patients' quality of life since it is painful, nonhealing and often without adequate response to the applied therapy, especially when it has not been recognised on time. BRONJ certainly requires attention and further investigation. Effective treatment could be achieved only if ethiopathogenesis was clarified.

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