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Risk Factors of Bisphosphonate-Associated Osteonecrosis of the Jaws: Review of the Literature

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Abstract: *Bisphosphonates (BP) are synthetic analogs of naturally occurring pyrophosphate compounds with high affinity to calcium crystals, which allows them to bind to bone hydroxyapatite and inhibit osteoclast-mediated cross-resorption. In the clinical practice BP have been used for several decades for the treatment of multiple myeloma, bone metastases, osteoporosis, Paget disease and others. In recent years, reports of Bisphosphonate-associated osteonecrosis of the jaws (BAONJ) have increased. Epidemiological and clinical studies on this topic summarize discussions and controversies of different expert groups on various aspects of the problem, one of which are the risk factors of its occurrence. The risk factor are link to the BP and the specifics of the treatment with these drugs, to anatomical specifics of the dento-alveolar area, dental diseases and their related dental procedures and treatments, and other risk factors such as different medications, comorbidities, risky health behavior, genetics and more. This suggests that BAONJ is an extremely complex and multifactorial process requiring careful monitoring and individual approach to each patient. BAONJ is considered an irreversible condition, and therefore efforts should be directed to its prevention both before and after the onset of BP therapy. The level of knowledge of dental practitioners, and medical specialist in general, about the risk factors of BAONJ, is crucial for the prevention of this complication.*

Keywords: *risk factors, knowledge, prevention, bisphosphonates, osteonecrosis*

Abbreviations: *BP - Bisphosphonates; BAONJ - Bisphosphonate-associated osteonecrosis of the jaw; SRE - Sceletal-related events; Zoledronate = Zoledronic acid; SNP - Single nucleotide polymorphisms; MHC - Major histocompatibility complex.*

1. Introduction

Bisphosphonates (BP) are synthetic analogs of naturally occurring pyrophosphate compounds with high affinity to calcium crystals, which allows them to bind to the bone hydroxyapatite and inhibit the osteoclast-mediated bone resorption[1]. In the clinical practice, BP has been used for several decades for the treatment of multiple myeloma, osteolytic bone metastases, osteoporosis, Paget disease, fibrous dysplasia, McCune-Albright syndrome, hypercalcemia of tumor origin and others [2,3,4,5,6]. After the first reported cases in 2003 [7] of a side effect associated with BP intake, named later Bisphosphonate-associated osteonecrosis of the jaws (BAONJ), every year in the scientific literature the reports of the problem increase in number.

BAONJ is defined as: "necrosis of the jaw bone, related or unrelated to dental procedures, persisting for more than 6 to 8 weeks, refractory to conservative treatment, in patients having no history of prior radiotherapy in the affected area, treated intravenously with amino-containing bisphosphonates for at least one year, or orally for a much longer period, for a general disease causing bone resorption" [8].

Epidemiological and clinical studies on this topic summarize discussions and controversies of different expert groups on many aspects of this complication, one of with are the risk factors. This suggests that BAONJ is an extremely complex and multifactorial process requiring careful monitoring and individual approach to each patient. BAONJ is considered an irreversible condition, and therefore efforts should be directed to its prevention both before and after the onset of BP therapy [9,10,11].

The literature mainly addresses several groups of risk factors:

2. Risk Factors Associated with the Treatment with Bisphosphonates

Type of BP: According to Danneman et al. cases of osteonecrosis of jaws reported up to 2006 are associated with the use of only amino-containing

bisphosphonates [3]. There is no absolute unanimity in the literature on which BP causes more frequent development of BRONJ, but scientific evidence supports the prevailing view that Zoledronic acid has highest risk-potential [10,11,12,13,14,15,16,17].

Route of Administration: The risk is higher with intravenous BP [10,11,13,17] than with oral BP, but this factor may be closely related to their widespread use in patients with malignant neoplasms that receive significantly higher overall doses and their treatment usually has longer duration [16]. According to the literature, the lower risk for oral BP intake is due to poor intestinal absorption (0.64%) [16].

Administration Schedule: Osteoclast precursors in the bone marrow, as well as in the human body as a whole, have remarkable recovery capacity. Sequential exposure to toxins spread over long time intervals is better tolerated than consecutive short inter-period exposures This is why the frequency of administration is also recognized as a risk factor by many oncologists who now prescribe intravenosus zoledronate every 3 or 6 months, which is different from the manufacturer's recommendation for 3 weeks to one month. This reduction in the frequency of administration has led to a decrease in the number and severity of the cases [17].

Corso and call. published a study on patients with multiple myeloma, divided into two groups: the first received bisphosphonate treatment under the standard monthly basis and patients in the second group received bisphosphonates monthly in the first year , and then - every three months. A statistical lower number of BAONJ cases was established in in the second group, while in the first group fcases of jaw necrosis were found after the first year of treatment. The authors reported that the index Sceletal-related events (SRE), measuring the condition of the bone as a whole was comparable in both groups [15].

Dose: It is well known that for almost any pharmaceutical product, increased dosing results in a greater effect, and respectively, to a greater and more significant severity of the complications. Available data shows a higher risk of developing osteonecrosis of the jaw by increasing the total dose of BP (both Zoledronate and Pamidronate) administered intravenously monthly to cancer and hematology patients [10]. There is insufficient follow-up data for intravenous administration of Zoledronate and Ibandronate (administered every 3, 6 to 12 months) in non-cancer patients [65]. Of the oral BP, Alendronate accounts for 95% of all BAONJ cases, whereas Residronate accounts for 3% and Ibadronate for 1%. This is considered to be due to the recommended dose of Alendronate at 70 mg/week, compared to Residronate at 35 mg/week and Ibadronate 150 mg / month, equivalent to 35 mg/week [17].

Duration of Treatment: The incidence of development of BRONJ is higher with longer treatment duration, especially when the duration of therapy exceeds four years. This period may be reduced by the presence of certain concomitant diseases, chronic glucocorti-costeroids, or co-administration of BP with angiogenesis inhibitors [11].

Bamias et al. believe there is a strict correlation between the duration of treatment with bisphosphonates and the manifestation of maxillary necrosis, and find that the average exposure period of the patients with BAONJ is 39,3 months (from 11 to 86 months) and the patients without BAONJ - 19 months (from 4 to 84.7 months), and the risk of developing the condition is 1%12 months after the start of treatment, and up to 11% in the fourth year of intake. The authors report that these data change depends on the type of bisphosphonate - in patients treated with Zoledronic acid alone the risk varies from 1% in the first year to 21% in the third year of treatment initiation, whereas in patients treated with Pamidronate (with or without Zoledronic acid) - the risk varies from 0% during the first two years of onset of treatment and up to only 7% after four years of treatment [12].

Corso et al. determine the following timing for development of BAONJ depending on the bisphosphonate used: Pamidronate necrosis was observed no earlier than 23 months after initiation of therapy; when applying Zoledronate this period of no less than 28 months; with combined use of Pamidronate and Zoledronate necrosis may be observed no earlier than 43 months after the onset of therapy [15].

Fung et al. report that in case of division by BP type, a time of 6.0 tears and 2.2 years is necessary, respectively, in oral administration of Alendronate and in intravenous Zoledronic acid therapy, for up to 50% of patients to develop BAONJ. After disease stratification, a treatment time of 5.3 years and 2.2 years is required, respectively for osteoporotic patients and for cancer patients, in order 50% of them to develop BAONJ [18].

Regarding the cumulative doses and the duration of treatment with oral BP, the majority of cases have been observed in patients treated for osteoporosis for years (usually more than 2-3 years), with an average of 4.6 years, according to Palaska et al, [19] They report that the average time for the occurrence of BAONJ when taking Zoledronate is 1.8 years, and the minimum is 10 months, and as for Pamidronate, the time is 2.8 years on average, with minimal time of 1.5 years. Unfortunately, sometimes there are cases of BAONJ after several BP infusions (most commonly after tooth extraction) [19].

Risk potential: Alendronate and Zoledronate have the highest potency and cause the majority of the cases of BRONJ [17].

3. Risk Factors Associated with the Dento-Alveolar System

3.1. Anatomical Comorbidity

The alveolar process, both in the lower and upper jaw, is the most vulnerable part**.** This is due to much greater complexity and speed of bone remodeling than normal in that area, as well as traumatic occlusion, and sometimes the pressure of dentures**.** Even cases of spontaneously occurring necrosis are within alveolar bone [17].

Mandible / Maxilla: Most of the studies based on a large number of cases show a tendency for BACCP to appear more frequently in the lower jaw than in the upper jaw (2: 1) [17]. Rarely, both jaws are affected. (4.5%). [13].

Torus: The mandibular torus, palatine torus and bone exostosis are places, that are more easily locally traumatization in the course of day-to-day activities, and are often affected [10,17]. Marx et al. already in their first publications on this topic reported development of BAONJ in 9.2% on mandibular toruses.16.Toruses are not just a risk factor but a very vulnerable place, because the bone surface in their regions is constantly undergoing remodeling. The thin mucus covering the torus contributes to this [17].

3.2. Dental Diseases / Procedures

Dental Procedures: According to the literature, the prevalence of bisphosphonate-associated osteonecrosis of the jaws associated with previous dental procedures is predominant compared to the so-called spontaneous BRONJ. Woo Sook-Bin et al. found that between 33% and 86% of the cases were manifested after various dental procedures [9].

Even in one of his first publications on the issue, Marx et al. [20] found that the most commonly associated with BAONJ dental problem was clinically expressed or radiologically established periodontitis - in 84% of patients. Dental caries in the area of necrosis were recorded at 28.6% [20]. Dental extraction [10,11,13,17] has the leading role - initiator in up to 62% of the cases [17].

Hyperoculsion/ Prosthetics: Excessive chewing forces initiate cases of BRONJ, due to the higher velocity and remodeling rates in the alveolar bones [17]. It is assumed that the mechanism of development of necrosis after putting dentures is analogous [10,13].

Periodontal Diseases: Active periodontal inflammation is associated with the development of osteonecrosis of the jaw in patients receiving BP [10,11,13,17]. This is due to further increased bone remodeling stimulated by the inflammatory process.

However, periodontal disease is usually observed in the general population in subjects> 40 years of age, which may be a confusing factor in the evaluation of the epidemiological association. Also, early clinical stages of BAONJ may include unexposed bone necrosis that can mimic clinical and radiological findings of periodontitis (dental mobility, loss of bone, loss of attachment or pus), which may lead to mistaken diagnosis and overestimation of the relationship between BAONJ and periodontal diseases [10].

Surgical Interventions in the Alveolar Bone: Surgical manipulations, other than tooth extraction - dental implants, endodontic, periodontal and peri-implant surgery, also increase the rate of bone remodeling and can therefore lead to the appearance of BRONJ [10,11,13,17].

4. Other Risk Factors

Chemotherapy: The immunosuppressive effects of chemotherapy have an adverse effect on the body and thus contribute to the occurrence of BAONJ [10,17].

Corticosteroids are associated with an increased risk of BAONJ [10,11,13,17]. This is due to impaired bone remodeling when treated with them.

Antiangiogenic Agents slow down oral repair processes and are a predisposing factor for BAONJ manifestation [13]. The combined use of the new generation of antiangiogenic agents (bevacizumab, sunitinib, sorafenib, denozumab) and BP is associated with an increased risk of developing BAONJ. There is also new evidence of increased incidence of BAONJ in cancer patients treated with tyrosine kinase inhibitors and bevacizumab. Intermittent data have been published regarding the role of thalidomide [10].

Age and Sex are variably reported as risk factors [10]. The higher incidence of this complication in the female population is probably a reflection of the underlying disease for which agents were prescribed (osteoporosis, breast cancer).

Some studies indicate an increase in the risk of developing BAONJ by 9% with each decade of age [17]. There are very limited data describing the occurrence of the complication in the pediatric population [10].

Geographical Epidemiology: The frequency of BAONJ may vary depending on the population studied. Reports from Greece and Turkey describe a much higher frequency than in Italy and the United States. The reasons for these differences could include differences in diagnostic criteria in these different regions as well as genetic factors. However, differences in dental hygiene and frequency of dental examinations may also be the main contributing factors to this geographical difference [11].

Smoking, Alcohol, Obesity: Tobacco use has been reported as a risk factor for BAONJ [10,11,13,17]. Smoking can be a confusing factor, given that smokers tend to have worse oral hygiene than non-smokers. The use of alcohol [10] and obesity [10,17] are also mentioned in some publications as risk factors.

Genetic Factors: In recent years, genetic factors have been given more attention to [13], although individual genetic predisposition to the development of BAONJ has been investigated only in a small number of scientific papers. Several reports describe single nucleotide polymorphisms (SNPs), located in many gene regions, associated with bone turnover, collagen formation, or certain metabolic bone diseases, that are associated with the development of BAONJ [11]. The largest study conducted so far (n = 94 cases) suggests that MHC class II polymorphisms may represent genetic risk factors associated with the development of this complication [10].

Type of Tumor: The type of tumor is reported as a risk factor [10,11,13,17]. The most frequently types of cancer are: multiple myeloma, breast, prostate, and lung cancer.

Accompanying Diseases: Hypocalcaemia, hyperparathyroidism, and bone mineral disturbances: one study shows the possible contributory effects of secondary hyperparathyroidism on the development of BAONJ. Over the past year, a strong relationship between osteomalacia and the BP-treatment complication has been identified. The triggering effect of vitamin D deficiency, secondary hyperparathyroidism and bone mineral defects have already been demonstrated in animal models and are currently under investigation [10]. Anemia, diabetes [10,17], systemic lupus, rheumatoid arthritis, etc. [10] are also referred to as risk factors for the occurrence of BAONJ. For some authors, diabetes does not necessarily results in the occurrence of BAONJ and should not be considered as a single risk factor. On the other hand, hyperglycemia as a possible indicator for poorly treated or still undetected diabetes is associated with BAONJ [21].

Conclusively, Abu-Id et al. [22] have proposed a predictive scale for risk of development of BRONJ:

1. At high risk: patients with malignancy receiving intravenous BP (Zoledronate or Pamidronate) and / or with a history of chemotherapy, radiotherapy or ongoing exogenous steroid use.

2. At low risk: patients receiving oral BP without a history of chemotherapy, radiotherapy or ongoing exogenous use of steroids (mostly patients with non-steroid-induced osteoporosis).

However, about 25% of the BAONC cases are considered spontaneous [17].

5. Conclusion

BRONJ is a complication, associated with BP intake, that seriously degrades the quality of life of many patients. As the condition is considered to be irreversible, and treatment options are still a complex and controversial subject among the clinicians, our efforts should be focused primarily to its prevention. For this, the knowledge of the epidemiology and the risk factors for the occurrence of BAONJ are of paramount importance. It is crucial to increase the awareness of dental practitioners, and medical specialists in general about this aspects of the problem in order to minimize the risk of developing this serious complication.

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