BISPHOSPHONATE-RELATED OSTEONECROSIS OF THE JAW A 3-YEARS RETROSPECTIVE STUDY OF FREQUENCY AND RISK FACTORS

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ABSTRACT

Purpose: To estimate the frequency of bisphosphonate-related osteonecrosis (BRONJ) in the Bulgarian population between 2015-2018 and the correlation with the type of bisphosphonates as risk factors associated with BRONJ development.

Materials and methods: A retrospective analysis of the official database from the national health insurance system was conducted. The total number of patients with developed BRONJ was estimated. The type of intravenous bisphosphonate administered was associated with the incidence of BRONJ.

Results: 3543 patients developed BRONJ during 2015 – 2018. The frequency of the condition is constantly increasing. The incidence of BRONJ among patients receiving ibandronate acid was significantly higher than patients on alendronic acid treatment ($p < 0.001$).

Conclusions: BRONJ is constantly increasing condition in the Bulgarian population among cancer patients, treated with intravenous bisphosphonates. Administration of Ibandronic acid can be used as a significant risk factor and a predictor for BRONJ development in those patients.

Keywords: Bisphosphonates, osteonecrosis, incidence, risk

INTRODUCTION

Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is still rare, but well known complication associated with bisphosphonates administration in patients with cancer-related conditions, bone metastases, osteoporosis and multiple myeloma [1]. While the potential of bisphosphonates to improve cancer-specific survival of patients remains controversial, they have a significant

positive effect on the quality of life for patients with advanced cancer. From the other side, BRONJ as the main complication resulting from intravenous administration of bisphosphonates adversely affects the quality of life. Oral and maxillofacial surgeons first recognized and reported cases of non-healing exposed bone in the maxillofacial region in patients treated with intravenous bisphosphonates. The first report describing osteonecrosis of the jaw was by Marx in 2003 [2]. Since then this condition has shown increasing interest by maxillofacial surgeons and dentists.

BRONJ is defined as an area of exposed bone in the maxillofacial region that does not heal within 8 weeks in a patient who is currently receiving bisphosphonate medication and has not had radiation to the head-neck region. The diagnosis is usually made clinically and confirmed by radiographs.

The 2014 update of a position paper from the American Association of Oral and Maxillofacial Surgeons recommended changing the name of bisphosphonate-related osteonecrosis of the jaw (BRONJ) to medication-related osteonecrosis of the jaw (MRONJ), owing to the increased number of maxillary and mandibular osteonecrosis cases that have been linked to other antiresorptive or antiangiogenic treatments [3].

Risk factors for MRONJ can be divided into 3 big groups:

1. Medication-related:

- The type and way of administration.

The risk for ONJ among cancer patients enrolled in clinical trials and assigned to *placebo* groups ranges from 0% to 0.019% (0-1.9 cases per 10,000 cancer patients) [4]. The risk of ONJ among cancer patients exposed to zoledronate ranges between 50-100 times higher than cancer patients treated with placebo [5, 6].

- Duration of medication therapy and dosage

Data that links the incidence of osteonecrosis of the jaw and its etiologic factors are limited, and the incidence of osteonecrosis of the jaw in the general population (i.e., those not taking bisphosphonates) is unknown. Evidence is insufficient to confirm a causal link between low-dose bisphosphonate use in osteoporosis with osteonecrosis of the jaw. Osteonecrosis of the jaw is primarily associated with high-dose bisphosphonate use in cancer patients. [7]

The incidence of developing BRONJ among cancer patients exposed to zoledronate or denosumab is 0.6 and 0.5% respectively at 1st year and 0.9 and 1.1% at 2 years.

2. Local factors. Tooth extraction or other dento-alveolar procedures such as implant placement or periodontal surgery are considered to be the major risk factors for developing BRONJ. In a retrospective study with a sample of 176 cancer patients on zolenronate therapy, 15% developed BRONJ after tooth extraction [8]. Presence of chronic periodontitis is another well-established risk factor.

3. Demographic and systemic factors. Age and sex, corticosteroids, tobacco use are factors, which are inconsistently reported to be significant risk factors.

The true incidence of bisphosphonate-related osteonecrosis of the jaw (BRONJ) has yet to be determined. There are few reports on the incidence rate of BRONJ, and the results have varied considerably in studies because

of the different diseases being treated, the population evaluated, and the statistical methods applied [7, 9, 10].

To our knowledge, there is no officially published data for the incidence of BRONJ in the Bulgarian population.

The aim of this study is to determine the frequency of BRONJ in Bulgarian patients and the correlation of its incidence with the type of bisphosphonate drug.

MATERIALS AND METHODS

A retrospective analysis of official documents from the Bulgarian National Health Insurance System between 2015 – 2018 was performed.

Disease frequency is reported as incidence (number of new cases per sample [or population] per year or prevalence (number of cases in the sample [or population] reported as a percentage).

Statistical analysis. The retrospective review of BRONJ cases per year, reported from the National Health Insurance System and the cumulative incidence was assessed with Fisher's test.

The association between administered bisphosphonates (alendronic acid, ibandronic acid and risendronate sodium) and BRONJ incidence and comparisons among groups was evaluated by chi-square, Wilcoxon and Kruskal-Wallis tests.

RESULTS

The total number of patients diagnosed with BRONJ in the period 2015 – 2018 (only the first 6 months of the year) is 3543 (fig. 1).

Fig. 1. Total number of patients with BRONJ for the period 2015 - 2018

The incidence of BRONJ in patients on intravenous bisphosphonates treatment is increasing from 2015 (used as a reference year) to 2017, followed by a small decrease in 2018. The reason for this decrease most probably is that presented and evaluated; data is only for the first 6 months

of 2018. If this rate of incidence of new cases is kept, the number of BRONJ cases only for 2018 will be almost doubled compared to 2015.

Prevalence of BRONJ, summarized in percentages, is presented in fig.2.

Fig. 2. Percentage change in BRONJ frequency during the 2015-2018 time period

There is an increase of 5.15% in the prevalence of BRONJ between 2016 and 2015; an increase of 8.75% between 2017-2015 and a decrease of 0.47% for the period 2018-2015. But this decrease is due to the fact that the analysis is carried only on data obtained from the first 6 months of 2018.

In 2015 96% of patients with BRONJ were treated with ibandronic acid; 1% had treatment with alendronic acid and 3% - with risendronate. The highest incidence of BRONJ is correlated with the administration of ibandronic acid, compared to treatment with the other 2 medications.

($p < 0.001$). In 2016, 901 patients were reported to develop BRONJ, and, again 95% of them had ibandronate treatment; 5% were on alendronate treatment, and not even 1 patient had risendronate treatment. In 2017 almost the same correlations were observed. 91% of 932 patients diagnosed with BRONJ had ibandronate treatment. Again no patients were on risendronate treatment, while the percentage of patients on alendronate is 10 times less than ibandronate treatment. In 2018 we had similar results with 93% of patients with developed BRONJ on ibandronate treatment (fig.3).

Fig. 3. Distribution of BRONJ associated with the type of administered bisphosphonate

DISCUSSION

The incidence of BRONJ in Bulgarian cancer patients who are treated with intravenous bisphosphonates seems to increase constantly within the limits of the time frame of this study.

The cumulative incidence reported in the literature varies considerable – from 1% to 9.64% [10, 11]. It ap-

pears to be lower in retrospective studies than in prospective studies. Anyway, the increasing tendency of BRONJ incidence in our study is consistent with the worldwide tendency of increasing the total incidence of this condition.

Bisphosphonates potency had an impact on the development of BRONJ. According to our results, adminis-

tration of ibandronic acid is associated with the highest risk for developing BRONJ. The prevalence is significantly higher than the prevalence of BRONJ in alendronate-treated patients. Our data support the fact that ibandronate acid administration is a significant risk factor and a predictor for the development of BRONJ in cancer patients.

However, results from other studies report that the more potent zoledronate had a 5-fold increased risk of BRONJ development compared with ibandronate [10]. Other studies report a risk of 5 -28-fold increase in relative risk for BRONJ development [12, 13]. Significant risk factors are also cumulative doses of bisphosphonates, oral health and dental extractions [14]. The type of bisphosphonate can be used as an important risk predictor for the development of BRONJ in oncologic patients.

Alendronate is associated with less than 10% BRONJ development. Currently, there is not enough data on the administration of risendronate and its association with BRONJ incidence.

The increasing frequency of BRONJ is a fact to be considered in the medical society in Bulgaria and especially among general dentists, who are often first to meet

such patients when they routinely seek dental help. Dentists must be aware of the clinical presentation of the disease. Because bisphosphonates have an important role in the management of cancer and metastatic bone diseases, they will be used in the future until a possible substitute with fewer side effects is launched. That is why dentists should focus on the proper management of dental and periodontal diseases before bisphosphonate treatment is initiated in order to prevent BRONJ and routinely control such patients in the course of their treatment.

We resume our results only as a pilot. The application of bisphosphonates, their treatment regimens and duration of application are strictly individual, and the guidelines are changing dynamically. That is why larger studies are needed to elicit many details in this area.

CONCLUSIONS

BRONJ is constantly increasing condition in the Bulgarian population among cancer patients, treated with intravenous bisphosphonates. Administration of ibandronic acid can be used as a significant risk factor and a predictor for BRONJ development in those patients.

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