Доклади на Българската академия на науките
Comptes rendus de l'Académie bulgare des Sciences
Tome 77, No 12, 2024

MEDICINE
Clinical medicine

STUDY OF THE INFLUENCE OF THE DURATION OF BISPHOSPHONATE INTAKE ON THE OUTCOME OF BISPHOSPHONATE-ASSOCIATED OSTEONECROSIS OF THE JAWS TREATMENT USING STATISTICAL METHOD LOGISTIC REGRESSION

Boryana Ilieva[1]✉, Krasimira Prodanova[2], Vassil Svechtarov[1]

Received on June 8, 2022
Presented by D. Damianov, Member of BAS, on November 29, 2022

Abstract

Bisphosphonates are a group of drugs that are widely used in the treatment of osteoclast-mediated diseases related to bone loss. Since 2003 the problem of bisphosphonate-associated osteonecrosis of the jaws (BAONJ) has been raised, and many authors have published the cases they have observed. BAONJ is a multifactorial disease, and the risk factors for the development of the disease can be divided into those related to bisphosphonate therapy, local risk factors, demographic and systemic factors, genetic factors and preventive factors.

The aim of the present study is to determine the effect of the duration of bisphosphonate intake on the outcome of bisphosphonate-associated osteonecrosis of the jaws (BAONJ) treatment using the statistical method one-dimensional logistic regression which is from the direction of regression analysis. In the present study we included 44 patients diagnosed with Bisphosphonate-associated osteonecrosis of the jaw (BAONJ). For each patient included in the study, information on the anamnesis, general and local status and results of clinical and paraclinical studies is recorded in an individual card.

Our study shows that with the increase of the duration of BF intake, the likelihood of disease progression also increases, found in the examination of the patient on the first and on the sixth month after the treatment of BAONJ. Therefore, we can conclude that the factor duration of BF intake can be used as a predictor of the outcome of BAONJ treatment, and with increasing of

https://doi.org/10.7546/CRABS.2024.12.13

its value, the likelihood of disease progression increases. Furthermore, we can suggest that the duration of bisphosphonate intake is an important factor that can lead to unfavourable clinical results in outpatient treatment of BAONJ.

Key words: osteonecrosis, bisphosphonate, jaw bones

Abbreviations: BF – Bisphosphonate, BAONJ – Bisphosphonate-associated osteonecrosis of the jaws, MRONJ – Medication-related osteonecrosis of the jaw

Introduction. Bisphosphonates are a group of drugs that are widely used in the treatment of osteoclast-mediated diseases related to bone loss, such as osteoporosis [1,2], multiple myeloma [3–5] , bone metastases in malignant tumors [6–9], Paget's disease [10], fibrous dysplasia [11] , osteogenesis imperfecta [12, 13].

In 2003, Marx [13] first described "painful exposure of the bone" of the jaws in patients taking pamidronate (Aredia, Novartis Pharmaceuticals) and zoledronate (Zometa, Novartis Pharmaceuticals). Since then, the problem of bisphosphonate-associated osteonecrosis of the jaws has been raised, and many authors have published the cases they have observed. BAONJ is a multifactorial disease, and the risk factors for the development of the disease can be divided into those related to bisphosphonate therapy, local risk factors, demographic and systemic factors, genetic factors and preventive factors [14]. The treatment of BAONJ can be divided into conservative and surgical, and there is no unanimity in the literature about the effectiveness of one or the other method of treatment. There is a lack of systematic data on the impact of risk factors for the development of BAONJ on the outcome of BAONJ treatment [15, 16].

The aim of the present study is to determine the effect of the duration of BF intake on the outcome of BAONJ treatment by using the statistical method one-dimensional logistic regression which is from the direction of regression analysis.

Material and methods. In the present study we included 44 patients diagnosed with Bisphosphonate-associated osteonecrosis of the jaw (BAONJ). For each patient included in the study, information on the anamnesis, general and local status and results of clinical and paraclinical studies is recorded in an individual card. Twenty (45.5%) of the patients included in our survey were women and 24 (54.5%) were men, minimum age 36 years, maximum age 88 years, mean 62 years. The present study shows that in 40 (90.9%) of the patients the main diagnosis was malignant disease, and in four patients (9.1%) the intake of BF was indicated by osteoporosis. In 32 (72.7%) patients the introduced BF was Zoledronic acid, in one patient (2.2%) it was Pamidronic acid, in two (4.5%) Ibandronic acid, in five (11.4%) Zoledronic acid and Pamidronic acid, in one patient (2.2%) Zoledronic and Alendronic acid, in two (4.5%) Alendronic and Ibandronic acid and one patient (2.2%) received Zoledronic, Ibandronic and Pamidronic acid. In four of the patients (9.1%) BF was taken orally, and in 40 patients (90.1%) it was administered intravenously. Our study showed a maximum value of the duration of BF 108 (in months), a minimum of 8 months, an average of 41.75 months.

The treatment methods applied to the patients we studied are surgical, conservative and surgical-conservative methods. The performed surgical interventions can be summarized in two surgical approaches: surgical debridement and sequestrectomy. The applied drug treatment can be divided into: Antibiotic treatment – the choice of antibiotic is in accordance with the recommendations of the American association of oral and maxillofacial surgeons (AAOMS) [7, 14]: Amoxicillin, in combination with Metronidazole; in patients with allergy to penicillin, the use of clindamycin or azithromycin is recommended [1]; Antimicrobial agents – Flagyl and use of antiseptic solutions – oral rinses with 2% chlorhexidine solution (Eludril, Corsodyl).

The outcome of the treatment depends on many factors, furthermore one of the main factors is the duration of BF intake, which has a direct impact on the effectiveness of treatment. The factor duration of BF intake is defined as the time from the start of BF therapy (first intake of BF-oral or intravenous) to the time the BAONJ is diagnosed. We reported the results of the treatment on the 30th day and on the 6th month. Periodic follow-up examinations were performed with a frequency determined by clinical symptoms and indications for treatment. Based on the BAONJ staging of AAOMS according to clinical manifestations, we divided the patients in the present study as follows:

- **At risk** – no apparent necrotic bone in patients who have been treated with oral or intravenous bisphosphonates;
- **Stage 0** – no clinical evidence of necrotic bone but nonspecific clinical findings, radiographic changes, and symptoms;
- **Stage 1** – exposed and necrotic bone or fistulas that probe to bone in patients who are asymptomatic and have no evidence of infection;
- **Stage 2** – exposed and necrotic bone or fistulas that probe to bone associated with infection as evidenced by pain and erythema in the region of exposed bone with or without purulent drainage;
- **Stage 3** – exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and one of the following: exposed and necrotic bone extending beyond the region of alveolar bone (e.g. inferior border and ramus in mandible, maxillary sinus, and zygoma in maxilla) resulting in pathologic fracture, extraoral fistula, oral antral or oral nasal communication, or osteolysis extending to inferior border of the mandible or sinus floor [17].

The analysis of clinical data shows that one patient (2.3%) was diagnosed in stage 0, four patients (9.1%) in stage 1, 33 patients (75%) in stage 2 and 6 (13.6 %) are in stage 3. In the present study the results were reported according to the following criteria:

- progression – transition to a more advanced stage of BAONJ;
- stationing – the patient is in the same stage of BAONJ at different intervals of documentation;
- clinical improvement – transition to a lower stage of BAONJ;
- remission – complete coverage of the exposed bone with intact oral mucosa, without clinical and paraclinical signs of inflammation.

After analyzing the data on the development of BAONJ in a follow-up examination after one month, we found the following distribution: in 15 (34.1%) patients there was a clinical improvement in the disease, in two (4.5%) there was progression of the disease, 26 (43%) of the patients have the disease stationing, and in one patient (2.3%) – remission. Regarding the development of the disease after 6 months, we found the distribution as follows: clinical improvement was observed in 11 (25%) patients, remission in six (13.6%), stationing in 20 (45.5%), and progression in seven (15.9%) patients.

Statistical method. The statistical method univariate logistic regression is used, which is from the direction of regression analysis. Regression analysis is a tool to develop a prediction model for predicting the effect of one or more variables or factors on a particular phenomenon. The variable which is to be explained or for which we need to develop a prediction model is called the dependent variable and the variable(s) which explains the dependent variable or factors is called the independent variable(s). If the number of independent variables is only one, then the model is termed a one-dimensional regression model. In case the number of independent variables is greater than one, then the model is termed a multiple regression model. The simplest regression model is the linear regression model, which is of the form

$$y = B_0 + B_1(X_1) + B_2(X_2) + \cdots + B_k(X_k),$$

where X_i's are the independent variables and y is the dependent variable. The regression coefficients B_i $(i = 1, 2, \ldots, k)$ reflect the degree of the influence that X_i's have on y. The objective is to determine the unknown coefficients in such a way that the sum of squares of errors in estimating y by the regression curve is minimized. The estimated coefficient $B_i > 0$ is interpreted as follows: increasing the values X_i of the independent variable leads to increasing the value of the dependent [11].

When the values y of the dependent variable are real numbers, i.e. it is quantitative to model the dependence applied linear or nonlinear regression analysis. When the dependent variable is dichotomous qualitative (two outputs: state A or state not A), logistic regression is used for modelling, and the independent variables (predictors) can be both quantitative and qualitative. In the univariate

logistic regression it is supposed that the probability of appearance of a state A depends of the model function $y = \exp(B_0 + (B_1)x)/(1 + \exp(B_0 + (B_1)x))$, where $\exp(x)$ is the so-called exponential function.

The aim is to detect if the factor x is prognostic, i.e. statistically significant. Wald's χ^2 test is used to infer about the significance of the fitted model. The hypothesis that it tests is: H0: The state of y is not affected by the variations of the values of x.

To test the null hypothesis H0, the level of statistical significance $p = 0.05$ is most often chosen. This is the probability of making an error of the first kind, namely to reject the null hypothesis (the factor is not predicative) when it is true.

Obtaining value $p < 0.05$ for the coefficient B_1 from Wald's χ^2 statistics, the null hypothesis is rejected and the hypothesis that the factor is statistically significant is confirmed, i.e. predicative. The method also gives a classification of false-positive and false-negative cases and the percentage of cases correctly predicted by the logistics model.

For statistical analysis of the data, a specialized statistical analysis package STATISTICA 11 [18, 19] was used. In our study, the dependent variable was the result of treatment of BAONJ, which assumes a state of "stagnation" and "progression". Two cases were considered for the dependence of the duration of BF intake:

1. The result of the treatment of BAONJ was reported one month after treatment.

2. The result of the treatment of BAONJ was reported six months after treatment.

The parameters of the constructed univariate logistics models for the dependence of BAONJ and the predictor "duration of BF intake" were evaluated.

Results and discussion. ***1. Analysis of the relationship between the duration of BF intake and short-term treatment outcomes reported on day 30.*** The parameters of the fitted logistic model are given in Table 1.

The obtained p-value of Wald's test for B_1 is $0.0368 < 0.05$, i.e. the null hypothesis for independence of BFSA, reported for one month, was rejected after treatment with the duration of BF intake.

The positive coefficient $B_1 = 0.0318$ of factor "DURATION" shows that with increasing duration of BF, the likelihood of disease progression increases, established in the first month after treatment.

The probability of appearance of a BAONJ progression, reported in the first month after treatment using constructed logistic model is calculated by the model function $y = \exp(-0.8924 + (0.0318)x)/(1 + \exp(-0.8924 + (0.0318)x))$, where the variable x is replaced by the value of the duration of BF intake.

Table 1

Estimated parameters of the logistic regression models for BAONJ and duration of BF intake, reported one month after the treatment

Model: Logistic regression (logit) N of 0's: 16 1's: 28 Dep. var: Development of BAONJ registered on the 1st month after the treatment
Loss: Max likelihood (MS-err. scaled to 1) Final loss: 26.184604062
$\chi^2(1) = 5.3132$, $p = .02117$

	Const. B_0	B_1 (Duration)
Estimate	−0.892438	0.03184031
Standard error	0.7280673	0.01525056
Wald's χ^2 p-value	0.0203219	0.03682261

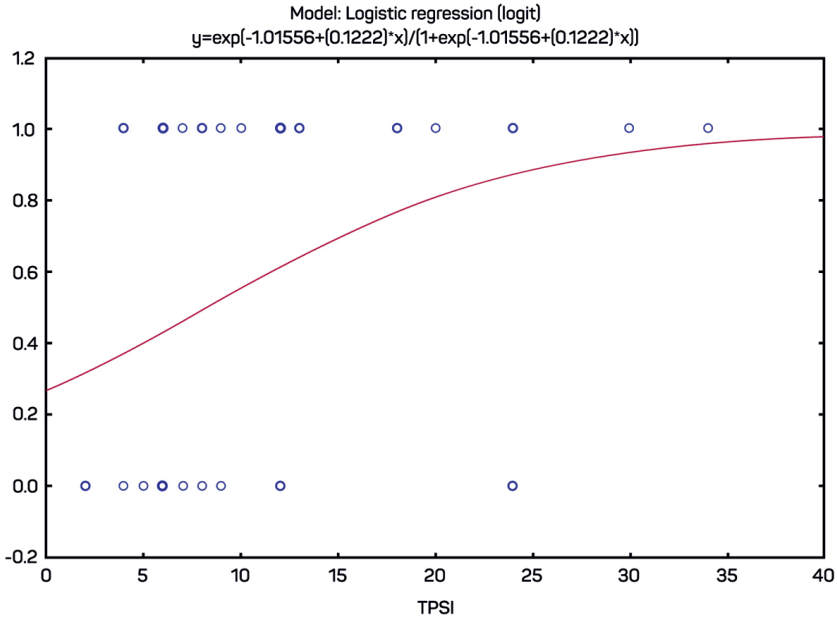

Fig. 1. Estimated probability distribution for progression of BAONJ, reported in the first month of treatment, associated with the duration of BF intake

For example, for a value of $x = 40$, there is a probability of progression of BAONJ in the first month of treatment equal to 0.6, i.e. 60%. It can be seen that the probability at duration of BF intake 10 months is 0.35 and increases to 0.96 at duration of 110 months.

2. Analysis of the relationship between the factors duration of BF treatment and the results of treatment of BAONJ, established at the sixth month. Analogously to item 1, it was found that the factor duration of BF treatment is a prognostic factor for BAONJ, reported six months after treatment because the p-value was $0.02 < 0.05$. The coefficient B_1 is positive (0.059). The estimated parameters are shown in Table 2.

Table 2

Estimated parameters of the logistic regression models for BAONJ and duration of BF intake, reported six months after the treatment

Model: Logistic regression (logit) N of 0's: 17 1's: 27 Dep. var: Development of BAONJ registered on the 6th month after the treatment
Loss: Max likelihood (MS-err. scaled to 1) Final loss: 23.920583098
$\chi^2(1) = 10.863$, $p = .00098$

	Const. B_0	B_1 (Duration)
Estimate	−1.323624	0.0593314
Standard error	0.715849	0.0248161
Wald's χ^2 p-value	0.0446306	0.01681549

Through the constructed logistic model, the probability of BAONJ progression can be predicted, reported six months after treatment, using the estimated coefficients $B_0 = -1.3236$ and $B_1 = 0.05933$. The probability is calculated by the fitted model function $y = \exp(-1.3236 + (0.05933)x)/(1 + \exp(-1.3236 + (0.05933)x))$, where the variable x is replaced by the value of the duration of BF intake.

The graph for the change in the probability of the presence of "PROGRESS" of the BAONJ, reported six months after treatment, depending on the duration of BF is presented in Fig. 2.

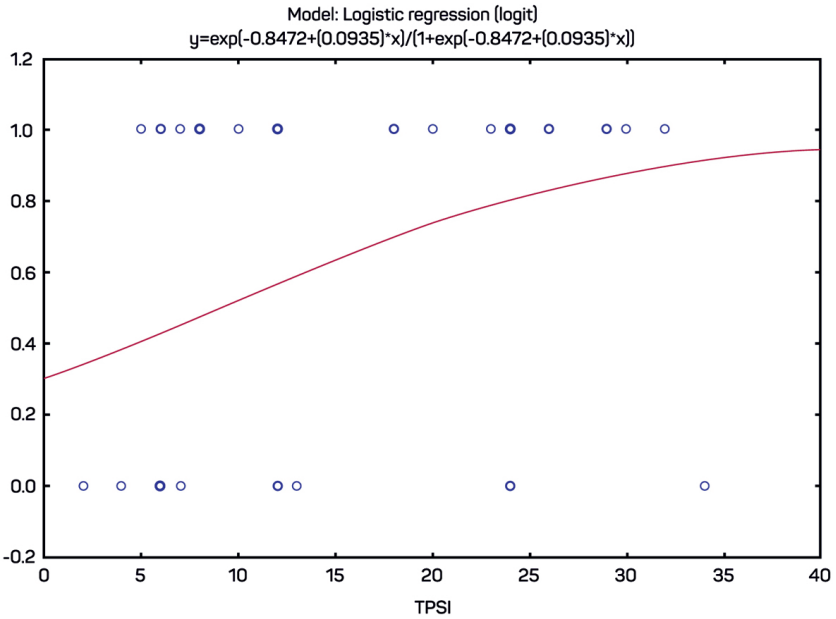

Fig. 2. Estimated probability distribution for progression of BAONJ, reported in the sixth month of treatment, associated with the duration of BF intake

It can be seen that the probability of progression of BAONJ, reported at the sixth month of treatment at duration of 10 months increases from 0.35 to 0.99 at duration of 100 months.

Our results are similar to the results of other authors published in the literature so far. According to Choi et al. [20] and AAOMS the factors that are best known to be related to the outcome of MRONJ (medication related osteonecrosis of the jawbone) are the duration of use of antiangiogenic or antiresorptive agents and the type of the drug.

Details of the ways in which drugs affect the incidence of MRONJ are provided in the American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw in 2014. In general, the incidence of MRONJ increases with increasing duration of drug administration [17], but there is little data in the literature on this subject.

Conclusions. Our study shows that as the duration of BF intake increases, so does the likelihood of disease progression, found in both the first and sixth months after treatment. From the comparison of the graphs it can be concluded that the duration of bisphosphonate intake is an important factor that can lead to unfavourable clinical results in outpatient treatment of BAONJ. Therefore, we can conclude that the factor duration of BF intake can be used as a predictor of the outcome of BAONJ treatment, and with increasing of its value, the likelihood of disease progression increases.

REFERENCES

[1] Office of the Surgeon General (US) (2004) Bone Health and Osteoporosis: A Report of the Surgeon General, Rockville (MD), Office of the Surgeon General (US). Message from Tommy G. Thompson (available from: `https://www.ncbi.nlm.nih.gov/books/NBK45522/`).

[2] Carey J. J. (2005) What is a 'failure' of bisphosphonate therapy for osteoporosis?, Cleve. Clin. J. Med., **72**(11), 1033–1039.

[3] Tiegs R. (1997) Paget's disease of bone: indications for treatment and goals of therapy, Clin. Ther., **19**(6), 1309–1329.

[4] Berenson J., B. Hillner, R. Kyle et al. (2002) American Society of Clinical Oncology Clinical Practice Guidelines: The Role of Bisphosphonates in Multiple Myeloma, J. Clin. Oncol., **20**(17), `https://ascopubs.org/doi/10.1200/JCO.2002.06.037`.

[5] Badros A., D. Weikel, A. Salama et al. (2006) Osteonecrosis of the jaw in multiple myeloma patients: clinical features and risk factors, J. Clin. Oncol., **24**(6), 945–952.

[6] Bamias A., E. Kastritis, C. Bamia et al. (2005) Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: Incidence and risk factors, J. Clin. Oncol., **23**(34), 8580–8587.

[7] Ruggiero S. L., T. B. Dodson, J. Fantasia et al. (2014) American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw – 2014 update, J. Oral Maxillofac. Surg., **72**, 1938–1956.
[8] Hillner B., J. Ingle, R. Chlebowski et al. (2003) American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer, JCO, **21**(21), 4042–4057.
[9] Body J. J. (2006) Breast cancer: bisphosphonate therapy for metastatic bone disease, Clin. Cancer Res., **12**(20 Pt 2), 6258–6263.
[10] Landesberg R., S. Eisig, I. Fennoy, E. Siris (2009) Alternative indications for bisphosphonate therapy, J. Oral Maxillofac. Surg., **67**(5 Suppl), 27–34.
[11] Devogelaer J. P. (2000) Treatment of bone diseases with bisphosphonates, excluding osteoporosis, Curr. Opin. Rheumatol., **12**(4), 331–335.
[12] Bohach S., K. Gibson, M. Warman et al. (2003) Intravenous bisphosphonate therapy in children with osteogenesis imperfecta, Pediatrics, **111**(3), 573–578.
[13] Marx R. E. (2003) Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: A growing epidemic, J. Oral Maxillofac. Surg., **61**(9), 1115–1117.
[14] Ruggiero S. L., T. B. Dodson, L. A. Assael et al. (2009) American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws – 2009 update, J. Oral Maxillofac. Surg., **67**(5 Suppl), 2–12.
[15] Hoff A. O., B. B. Toth, K. Altundag et al. (2006) Osteonecrosis of the jaw in patients receiving intravenous bisphosphonate therapy, J. Clin. Oncol., **24**(18), 8528.
[16] Ruggiero S. L., B. Mehrotra, T. J. Rosenberg, S. L. Engroff (2004) Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases, J. Oral Maxillofac. Surg., **62**(5), 527–534.
[17] American Dental Association Council on Scientific Affairs (2006) Dental management of patients receiving oral bisphosphonate therapy: expert panel recommendations, J. Am. Dent. Assoc., **137**(8), 1144–1150.
[18] StatSoft, Inc. (2011) STATISTICA Manual (Data analysis software system), Version 11.0.
[19] Jobson J. D. (1991) Multivariate Data Analysis, vol.1,2, Springer Ver.
[20] Choi N. R., J. H. Lee, J. Y. Park, D. S. Hwang (2020) Surgical treatment of medication-related osteonecrosis of the jaw: a retrospective study, Int. J. Environ. Res. Public Health, **17**(23), 8801.

[1]*Department of Dental, Oral and Maxillofacial Surgery, Faculty of Dental Medicine, Medical University – Sofia, 1 St. Georgi Sofiiski St, 1431 Sofia, Bulgaria*
e-mails: dr.ilieva@abv.bg, vassilsvechtarov@yahoo.com

[2]*Technical University of Sofia, 8 Kliment Ohridski Blvd, 1797 Sofia, Bulgaria*
e-mail: kprod@tu-sofia.bg