Bisphosphonate-associated Osteonecrosis of the Jaws: a Survey of the Level of Knowledge of Dentists about the Risks of Bisphosphonate Therapy

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Received: 04 June 2018
Accepted: 27 Nov 2018
Published Online: 31 Dec 2018
Published: 30 June 2019

Key words: survey, knowledge, dentists, bisphosphonates, osteonecrosis


INTRODUCTION

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 clinical practice BP have been used for several decades in the treatment of multiple myeloma, bone metastases, osteoporosis, Paget disease and some other conditions.¹-⁵ In recent years, reports of bisphosphonate-associated osteonecrosis of the jaws (BAONJ) have increased, especially in cases of oncological patients receiving intravenous BP. Epidemiological and clinical studies on this topic summarize discussions and controversies of different expert groups on the definition, epidemiology and risk factors, pathophysiology, classification, clinical manifestations, treatment and prevention of this complication. 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.⁶-⁸ The level of knowledge of dental practitioners about the risks of BP treatment is crucial for the prevention of this complication.

Introduction: Bisphosphonate-associated osteonecrosis of the jaws (BAONJ) is a side effect of treatment with bisphosphonate (BP). Reports of this complication have increased recently.

Aim: To evaluate the level of knowledge of dentists from Plovdiv, Bulgaria, about possible complications of bisphosphonate therapy of patients in dental practice.

Materials and methods: Three hundred and twenty-three dental practitioners from Plovdiv, Bulgaria, took part in an anonymous survey containing 25 questions, designed to evaluate the knowledge of dentists about the complications of BP therapy.

Results: Oral and maxillofacial surgeons have the best knowledge about the indications and side effects of BP therapy, while dentists with a specialty in Pediatric Dentistry and General Dentistry have insufficient knowledge. Of the respondents, 17.03% are absolutely uninformed about BP and their side effects, and 1/2 declare that they have never had a patient with complications from BP therapy in their practice, probably due to a lack of awareness of the problem. Approximately half of the dentists we surveyed agree to carry out prophylactic examinations of patients receiving BP and know what the prophylactic examination includes. Only 15.48% of the respondents have correctly responded that in order to be treated as clinically healthy, patients should have stopped taking BP for more than 10 years.

Conclusion: With the exception of specialists in Oral and Maxillofacial Surgery, dental practitioners in Plovdiv and the region are poorly informed about the complications associated with BP therapy. Therefore, efforts must be made to make these dentists better informed about BAONJ, especially about the methods and means of preventing this condition.
and, in the cases of an already emerging lesion, for timely diagnosis and proper referral of patients to a specialist.

AIM
To evaluate the level of knowledge of dentists from Plovdiv, Bulgaria, about possible complications of BP therapy of patients in dental practice.

MATERIALS AND METHODS
Between April and June 2017, 323 dental practitioners from Plovdiv, Bulgaria took part in an anonymous survey containing 25 questions designed to evaluate the level of knowledge of dentists about the complications of application of BP therapy* (See questionnaire below).

At first, 400 paper-based questionnaires were distributed and via the web site of the Bulgarian Dental Union in Plovdiv, 987 dentists were sent a link to an online version of the questionnaire made using Google forms. Additionally, 67 links were sent to dental practices that had provided their e-mail addresses online and the link was published in different dental groups on social networks. At the end of this period, 270 paper questionnaires and 53 digital questionnaires (a total of 323) meeting the inclusion criteria were collected.

Continuous variables were presented as median ± IQR or mean ± SD. Categorical variables were expressed as counts and percentages. Student’s t-test or Mann-Whitney U-test was used to compare means, as appropriate. Proportions were compared by the chi-square test. A p value <0.05 was considered statistically significant. All descriptive and analytic statistics were calculated using IBM SPSS Statistics v.24.

RESULTS
The median age of the 323 dental practitioners involved was 40 years (IQR=12). The gender distribution shows a significantly higher proportion of women (p<0.05).

The majority of respondents work in private dental practice (41.18%, n=133), followed by a group practice/dental clinic (33.13%, n=107), with no statistically significant difference noticed (p>0.05).

Of the participants in the survey, 18.58% (n=60) are lecturers from the Faculty of Dental Medicine at the Medical University of Plovdiv. The median duration of clinical practice was 15 years (IQR=16).

More than half of the participants (47.68%, n=154) have a specialty or are in the process of acquiring one (12.69% n=41), with the highest share being the specialists in General Dentistry (38.89%, n=63), Oral Surgery (21.60%, n=35) and Prosthodontics (14.20%, n=23). There is a statistical association and dependence between years of clinical practice and the absence or presence of a specialty ($\chi^2=135.077$, p=0.000). Of the dental practitioners who have specialty, the lowest relative share is comprised of those with up to 4 years of clinical experience, and the highest consists of dentists with experience of over 25 years.

Nearly 70% of the dentists know that BP are used in the treatment of osteoporosis (69.97%, n=226) and bone metastases (68.42%, n=221). 16.72% of the respondents wrongly state that BP are applied to patients with diabetes, arterial hypertension or rheumatoid arthritis. Over 80% of them know that BP target the jaw bones, but 1/5 of the surveyed dentists mistakenly answer that they affect the salivary glands or the hard dental tissues.

The major source of information on the possible complications of BP treatment for 24.46% (n=79) of the respondents was their studies at the Faculty of Dental Medicine, which correlates with the fact that they have 1 to 14 years of dental practice. Only 17.34% (n=56) have found out about the problem from medical or dental literature. Just 6.50% (n=21) of the dentists have been informed during training courses. A large part of dentists (17.03%, n=43) were informed about BAONJ for the first time from this survey. The participants state that dental /medical journals and books - 64.71% (n=209), followed by the Internet - 55.11% (n=178), are the most preferred sources for continuing their education on the problem.

Only 32.31% (n=105) of the dentists know that the intravenous application of BP pose a great risk to the patients. The results demonstrate the lack of knowledge of the importance of the route of BP administration into the body, with 2/3 of respondents not knowing that IV administration of BP is one of the risk factors for developing BAONJ.

From the respondents who answered correctly, the specialists in oral surgery (OS) and maxillofacial surgery (MFS) are with the highest rates, and those with pediatric (PD) and general dentistry (GD) are with the lowest rates. This recurrent tendency of high level of knowledge regarding BAONJ in the group of dental practitioners with specialty in OS and MFS and poorly informed PD and GD specialist is also observed in most of the following questions and answers (Table 1).
Table 1. Level of knowledge about BP therapy amongst wide pool of dental specialists.

<table>
<thead>
<tr>
<th>Specialty</th>
<th>OS</th>
<th>MFS</th>
<th>PE</th>
<th>OR</th>
<th>EN</th>
<th>PR</th>
<th>PD</th>
<th>GD</th>
<th>Other</th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td>n</td>
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<td>11</td>
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<tr>
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<td>100.00</td>
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<td>77.78</td>
<td>7</td>
<td>58.33</td>
<td>9</td>
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<td>5</td>
<td>55.56</td>
<td>3</td>
<td>33.33</td>
<td>2</td>
<td>16.67</td>
<td>3</td>
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<td>Jaws</td>
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<td>97.14</td>
<td>9</td>
<td>100.00</td>
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<td>88.89</td>
<td>10</td>
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<td>9</td>
<td>100.00</td>
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<td>88.89</td>
<td>8</td>
<td>88.89</td>
<td>11</td>
<td>91.67</td>
<td>11</td>
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<td>Other surgical manipulations</td>
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<td>9</td>
<td>100.00</td>
<td>6</td>
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<td>8</td>
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<td>31.43</td>
<td>7</td>
<td>77.78</td>
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<td>0</td>
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<td>3</td>
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<tr>
<td>IV</td>
<td>23</td>
<td>65.71</td>
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<td>88.89</td>
<td>4</td>
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<td>25.00</td>
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<td>Equally risky</td>
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<td>11.11</td>
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<td>22.22</td>
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<td>8.33</td>
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<td>6</td>
<td>17.14</td>
<td>1</td>
<td>11.11</td>
<td>2</td>
<td>22.22</td>
<td>2</td>
<td>16.67</td>
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<td>5-10 years</td>
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<td>14.29</td>
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<td>1</td>
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<td>2</td>
<td>16.67</td>
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<tr>
<td>Over 10 years</td>
<td>13</td>
<td>37.14</td>
<td>7</td>
<td>77.78</td>
<td>1</td>
<td>11.11</td>
<td>1</td>
<td>8.33</td>
<td>2</td>
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<tr>
<td>Not sure</td>
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<td>17.14</td>
<td>1</td>
<td>11.11</td>
<td>4</td>
<td>44.44</td>
<td>6</td>
<td>50.00</td>
<td>10</td>
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</table>

Only 29.41% (n=95) of dental practitioners report that they have patients with BAONJ in their practice. Most of the dentists (54.49%, n=176) have not encountered such patients and 16.10% (n=52) were unsure, probably due to the lack of experience or inability to diagnose this complication. Of the dental practitioners with a specialty, expectedly, all of the maxillofacial surgeons (MFS) and 3/4 of the oral surgeons (OS) have patients with BAONJ in their practice. One third to one fourth of the dentists with other specialities (excluding pediatric dentistry) also declare having such patients. It’s positive that 73.60% (n=237) will refer a patient with complications to the right specialist – OS or MFS.

With the highest relative shares are the dentists who state correctly that tooth extraction, implant placement and other surgical manipulations hide the greatest risk for patients on BP therapy. Only 14.86% (n=46) know that removable dentures can trigger the development of BAONJ and just about 1/5 of prosthetists note it.

Only 48.92% (n=158) of the respondents know that prophylactic examination of patients on BP therapy includes clinical examination and imaging. Again, only half are willing to conduct such examinations. Just 15.48% (n=50) of the dentists know that it takes 10 years for a patient to be considered clinically healthy regarding risk dental manipulations, after stopping the intake of BP.

DISCUSSION

Dental practitioners in Plovdiv and the region, with the exception of the specialists in Oral Surgery and Maxillofacial Surgery, are not sufficiently informed about BAONJ. We have found an improved level of knowledge of some aspects of the problem, compared to our first study on the problem, but still insufficient knowledge of many others. In some cases, the results correlate with the foundlings of other authors, whilst in others, there are significant differences.

We define a high level of knowledge when close to and above 70% of our respondents have answered correctly:

1. More than 2/3 of the respondents in our study correctly showed two of the main indications for therapy, osteoporosis and bone metastases, whereas in a previous survey on this problem, we found that less than 1/3 of the respondents (25.81%) were correct in pointing at these two indications. We report a significant improvement in the level of knowledge among dentists in Plovdiv about this aspect of the problem. Other researchers have similar results - 93.2% of the respondents have correctly stated that BP are used when treating patients with osteoporosis, but only half (47.9%) noted that bone metastases are also an indication for these medications. In a study in the United Arab Emirates (UAE) the majority of participants (68.4%) identified osteoporosis as the commonest indication for BPS treatment, but only 5.9% reported cancer as another major indication to take the medicine.

2. BPs target the bone system and in particular the jaw bones, indicated by most of the responders. This positive result is doubled compared to 41.12% in our previous study. Other studies have shown poorer knowledge of this topic -- 60% in Canada, 50% of the dental students and 68.36% of the dental practitioners in Brazil do not recognize BAONJ as a side effect of BP intake. In Korea, 56.5% of the respondents have heard of bisphosphonates as a group of medications associated with jaw bone disease, but only 31.4% routinely record BP intake when taking a patient’s history. In the UAE about sixty percent of participants regarded BRONJ as the most serious side effect of the drugs. In North Wales, 43.8% of dental practitioners have reported BAONJ as a possible complication.

3. In our study, most of the respondents knew what the risk dental procedures when treating patients receiving BP are, which we attribute to the relatively high number of participants with specialty in Oral and Maxillofacial Surgery. Other researchers have reported lower rates of 48.90% of knowledge of the issue, whereas in Spain, most of the participants have correctly identified the risk factors. Authors in the UAE state some gaps in the knowledge on the topic, with around one third of participants not aware of any relationship between BP therapy and dental treatment interventions. Hajmohammadi et al. have found that only 20% have good knowledge of the high risk procedures on dental patients taking BP, and 50.9% have just moderate knowledge. Gonzales et al. report that most participants in their study would avoid invasive procedures on patients taking any form of BP. Rosella et al. reported that dental students’ knowledge about how invasive dental treatment might be carried out in patients under therapy was not adequate. These knowledge gaps may lead to situations where patients receiving intravenous BP are treated too invasively and pa-
tients receiving low doses of oral bisphosphonates are not treated correctly.17

4. A patient with complications of BP therapy should be referred to an OS or MFS, which the majority of our respondents know. Nastro et al. highlight the important role of these specialists and point out that their intervention should not be underestimated.19 In all cases, treatment should be conducted jointly with the bisphosphonate-prescribing specialist - oncologist, hematologist, endocrinologist, or another.19 Gonzales et al. report that most participants in their study would direct patients requiring invasive dental treatment to an appropriate specialist.17

5. In our study as well as in others, it is stated that OS and MFS have better knowledge about BAONJ than other dentists who participated in the survey.10,11 This high level of knowledge of the specialists in Oral Surgery and Maxillofacial Surgery is the result of a good theoretical training combined with practical work. This is the reason these specialists are the main participants in other more elaborated and specific surveys on the topic.20 Also, we consider the differences in some results between our and other studies to be mainly due to the relatively high percentage of oral and maxillofacial surgeons who participated in our survey.

We define a low level of knowledge when close to or under 50% of our respondents have answered correctly:

1. The significance of the route of administration of BP into the body as a risk factor for BAONJ was noted by only 1/3 of respondents. Gaps in the dentists’ knowledge about the dangers that the different ways of application the BP drugs hide have also been found in Texas17 and the UAE11.

2. The importance of the intravenous administration of BP as a risk factor for BAONJ is known by only 1/3 of the dentists. The majority of the authors consider the risk of complications to be higher when these drugs are administered into the bloodstream.7,8,21,22

3. The significance of removable dentures as a risk factor is indicated by a total of only 15% of dentists and about 20% of prosthodontists, despite the fact that many authors have declared this manipulation as risky for patents on BP therapy.7,8,21

4. The majority of dentists in our study have not encountered patients with BAONJ in their practice or were unsure, which correlates with the findings in the UAE.11

5. Only half of the respondents gave a valid definition of a prophylactic examination of a patient receiving BP and when asked whether they are willing to perform prophylactic examinations of these patients, nearly half of the dentists would not or were not sure, which correlates with Vinitzky-Brener’s research that found that 50% of the professionals did not feel comfortable treating patients on BP therapy.23 The study in Ontario, Canada, also states that about 50% of dentists do not feel confident when treating a patient with BAONJ.10 Bone24 found that only 14.7% would deal with patients with BP complications. In UAE nearly 1/3 of the respondents were not aware of the ‘standard’ dental treatments for a patient on BP.11 Tanna et al. state that just over 40% of GD were confident to treat patients on oral bisphosphonates in primary care.25 This results in our and other studies we attribute to insufficient knowledge and experience of most practitioners on the proper prophylaxis and treatment of such patients, due to, as also stated by Tanna et al. lack of accessible guidelines and unclear protocols.

6. The time for a patient to be considered clinically healthy regarding risk dental manipulations after stopping the intake of BP is 10 years, as these drugs get attached to Ca2+ in the areas of high bone resorption, remaining integrated into the bone for more than 10 years.26 This fact is known by just 15% of the participants in the survey.

7. Poor knowledge of most aspects of the problem was found amongst dental practitioners of PD and GD, whereas other authors report that orthodontists (37%) are the least aware.11 Pediatric dentistry and orthodontic specialists usually treat younger patients, which is possibly the main reason for the gaps in their knowledge of BAONJ due to the complication being most common in senior patients.

Level of knowledge/recognition of the problem:

1. Evidence of the importance of the process and its growth as a problem in modern oncology and dentistry is the fact that, compared to our previous study,9 there is an increase in the number of dental practitioners who have encountered BAONJ. According to a study in Texas, the United States, about half of the dental practitioners have seen at least one case of BAONJ in their practice, which could be interpreted as a better recognition of the problem.24

2. Both we and other authors find that dental specialists prefer to get information from scientific publications.10 The first source of information on BAONJ in our study as well as the study of
Rosella et al.\textsuperscript{18} was university, followed by reading scientific papers, but the authors state that even though ninety-nine percent of dental students in their study declare to know BPs and identified the importance to report the use of BPs, only one fourth of 4-year students and one third of 6-year students knew the correct definition of BAONJ and half of the students did not recognize any active principle or commercial name of BPs, which shows some alarming educational gaps.\textsuperscript{18}

3. We have noticed a tendency for better knowledge about the problem of doctors with shorter length of service (up to 4 years). Other authors also found that dental practitioners with less than 5 years of clinical experience were significantly better informed on the subject.\textsuperscript{13} In this regard, it should be noted that BAONJ is a relatively new problem, reported for the first time in 2003 by Marx\textsuperscript{27} and Migliorati\textsuperscript{28}, and professionals with more than 15 years of experience did not have the opportunity to study this complication during their dental education. Most of the GD in our study have practiced dentistry for more than 15 years and have also shown poor knowledge of some aspects of the problem, which we partially attribute to the previously stated fact.

**CONCLUSIONS**

With the exception of the specialists in Oral Surgery and Maxillofacial Surgery, dental practitioners in Plovdiv and the region are not well informed about the application of BP and the risks associated with them, which requires efforts to be made to promote awareness and knowledge of BAONJ and especially the methods and means of its prevention.

Led by the importance and relevance of the issue at stake, we recommend enriching the amount of information taught to dental students as well as including BAONJ as part of the postgraduate studies, not only in Oral Surgery and Maxillofacial Surgery, but also in all other dental specialties, especially Pediatric Dentistry (we should note that they also treat adults) and General Dentistry as well as a wide range of medical specialties. Dental and medical journals, scientific forums, conferences and congresses listed as preferred sources of information should publish and present more studies and surveys on the issue, which should also be easily digitally accessible.

Therefore, every physician, and especially every dentist, should be aware of and be able to diagnose BAONJ as well as to promote the methods for prevention of this serious complication.

**REFERENCES**


* Questionnaire

Evaluation questionnaire of the level of knowledge of dentists about the complications of administration of BP therapy.

1. Gender: M F

2. How old are you? ........ years.

3. Where is your primary place of work?
   1. Faculty of Dental Medicine (FDM)
   2. Clinic of Maxillofacial surgery
   3. Non-dental department of the Medical University
   4. Independent dental practice
   5. Group Dental Practice / Dental Clinic
   6. Other

4. How many years of work experience do you have as a dental practitioner?
   ........ years

5. Do you have a specialty?
   1. Yes
   2. No
   3. In the process of acquiring one

6. What is your specialty (you already have or are in the process of acquiring one):
   1. Oral Surgery
   2. Maxillofacial Surgery
   3. Periodontology
   4. Orthodontics
   5. Endodontics
   6. Ortopedics
   7. Pediatric dentistry
   8. General dentistry
   9. Other

7. Do you know what bisphosphonates (BP) are used for?
   1. I am familiar with the purpose and use of these drugs
   2. I have heard of them
   3. I’m not familiar

8. BP are used in the treatment of:
   1. Osteoporosis
   2. Bone metastases
   3. Diabetes
4. Paget’s disease  
5. Arterial hypertension  
6. Rheumatoid arthritis

9. Are you familiar with the side effects of BP therapy?  
1. Yes  
2. No  
3. I’m not sure

10. What dental side effects do BP have?  
1. Affect soft tissues  
2. Affect jaw bones  
3. Affect the salivary glands  
4. Damage to the hard dental tissues  
5. Cause periodontal diseases

11. How/where did you first learn about the possible complications of BP treatment?  
1. This survey  
2. University  
3. Dental specialization  
4. Dental training courses  
5. Scientific forums and conferences  
6. Dental / medical journals and books  
7. Internet

12. In your opinion, after what amount of time do side effects of BP therapy occur?  
1. In less than 1 year  
2. After 1-2 years  
3. After more than 2 years  
4. Duration does not matter  
5. I’m not sure

13. Is the way of administration of BP relevant to increasing the risk of complications?  
1. Yes  
2. No  
3. I’m not sure

14. In your opinion, which route of administration of BP in the body has a greater risk?  
1. Oral  
2. Intravenous  
3. Intramuscular  
4. Equally risky  
5. I’m not sure

15. Have you encountered patients with complications after BP treatment in your dental practice?  
1. Yes  
2. No  
3. I’m not sure

16. On average, how many patients with symptoms or diagnosed complications of BP therapy do you encounter in your dental practice annually?  
1. None  
2. 1-2 patients  
3. 3-4 patients  
4. 5-10 patients  
5. More than 10 patients

17. Is dental examination necessary prior to initiating BP therapy?  
1. Yes  
2. No  
3. I’m not sure

18. Are you aware of the risk, associated with dental treatment in patients on BP therapy?  
1. Yes  
2. No  
3. I’m not sure

19. Of the list below, please indicate the high risk procedures on dental patients taking BP:  
1. Tartar removal  
2. Tooth extraction  
3. Implant placement  
4. Other surgical manipulations  
5. Endodontic treatment  
6. Treatment of caries  
7. Removable dentures  
8. Installing non-tightening dentures  
9. Orthodontic treatment

20. Do you know what the regular prophylactic examination of a patient on BP therapy consist of?  
1. Yes  
2. No  
3. I’m not sure

21. Please, note what the prophylactic examination of a patient on BP therapy includes:  
1. Clinical examination  
2. Clinical examination and imaging studies  
3. Clinical examination and biopsy of target tissues  
4. Clinical examination + imaging studies + biopsy

22. Would you perform prophylactic examinations on patients on BP therapy?  
1. Yes  
2. No  
3. I’m not sure

23. How long after completion of BP intake can patients be treated as clinically healthy in terms of risky dental treatment?  
1. 1 year  
2. 2-5 years  
3. 5-10 years  
4. Over 10 years  
5. I’m not sure

24. If you have any doubts that your patient has complications associated with BP treatment, what type of specialist would you refer them to?  
1. His GP  
2. Periodontologist  
3. Oral / maxillofacial surgeon  
4. Endodontics  
5. Orthopedics  
6. Orthodontic
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from BP therapy?
1. Dental training courses
2. Scientific forums and conferences
3. Dental / medical journals and books
4. Internet

7. Oncologist
8. I’m not sure

25. From the options listed below, which do you prefer to continue your education of the complications

2. Scientific forums and conferences
3. Dental / medical journals and books
4. Internet