

Investigation of the Approach of Dentists in Ankara to Patients Who Use Drugs as Bisphosphonates, Denosumab and Similar

Ankara'daki Diş Hekimlerinin Bifosfonat, Denosumab ve Benzeri İlaç Kullanan Hastalara Yaklaşımlarının Değerlendirilmesi

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ÖZET

Amaç: Bifosfonat, denosumab ve benzer yan etkilere sahip ilaçların osteoporoz, kanser ile ilişkili kemik metastazları ve Paget hastalığı gibi kemik ile ilişkili hastalıklarda kullanımının artması ile ilaçla ilişkili osteonekroz (Medication-Related Osteonecrosis of the Jaws, MRONJ) tablosunun görülme sıklığı da artmaktadır. Bu sebeple söz konusu ilaçları reçete eden tıp hekimlerinin ve diş hekimlerinin ilaçların kullanım alanları, etki mekanizmaları, ortaya çıkabilecek komplikasyonları konusunda gerekli bilgi ve donanımına sahip olmaları gerekmektedir.

Gereç ve Yöntem: Bu çalışmada Ankara'da hizmet veren diş hekimlerinin MRONJ ile ilgili bilgi düzeylerinin ve yaklaşımlarının değerlendirilmesi amaçlanmıştır. Bu amaçla çalışmada diş hekimlerine web-tabanlı anket ve yüz yüze görüşme metodu olarak 2 farklı yaklaşım uygulanmıştır. Çalışmada 130 kişi web-tabanlı ankete, 173 kişi ise yüz yüze ankete katılmıştır.

Bulgular: Tüm cevaplar değerlendirildiğinde bifosfonat, denosumab ve benzer yan etkilere sahip ilaçların osteonekroza sebep olabileceğinin farkındalığının %94.1 (285 kişi) oranında olmasına ve osteonekrozun en sık hangi çenede görüldüğü sorusuna %74 oranında doğru cevap verilmesine rağmen bu tür ilaçların kullanım endikasyonlarında doğru cevap oranının %6.6'yı geçmediği görülmüştür. Osteonekrozun teşhisi konusunda %25 olan doğru cevap oranının bu tür ilaçları kullanan hastalara risk oluşturacak tedavi yaklaşımlarının bilinirliğinde %7.9'a düştüğü görülmüştür.

Sonuç: Çalışmanın sonuçları değerlendirildiğinde, hem diş hekimliği eğitimi sırasında, hem mezuniyet sonrası sürekli eğitim yapılarak diş hekimlerinin MRONJ konusunda bilgi düzeylerinin artırılmasının gerekli olduğu sonucuna ulaşılmıştır.

Anahtar kelimeler: Bifosfonat; Denosumab; MRONJ; Osteonekroz

ABSTRACT

Aim: Increased use of bisphosphonates, denosumab, and other drugs with similar side effects, which are prescribed for osteoporosis, cancer-related metastases and bone-related diseases like Paget's disease, have resulted in an elevated frequency of Medication-Related Osteonecrosis of the Jaw (MRONJ) cases. Thus, medical doctors and dentists who prescribe these drugs should have full knowledge about their indications, mechanisms of action and complications caused by these drugs.

Material and Methods: In this study, we aimed to assess the knowledge of dentists who work in Ankara, Turkey, on the correct procedures and approach they would apply when treating patients with MRONJ. We used two approaches for this purpose: a web-based survey and face-to-face interviews with dentists. 130 subjects filled the online survey and 173 subjects were interviewed.

Results: The overall responses showed that despite 94.1% (285 subjects) know that bisphosphonates, denosumab, and other drugs with similar side effects may cause osteonecrosis of the jaws, and 4% of them correctly answering the question "which jaw is more likely to be affected by osteonecrosis of the jaw," only 6.6% accurately answered questions about the indications of such drugs. While 25% of the participants correctly answered the questions regarding the diagnosis of MRONJ, only 7.9% of them knew all the dental treatments which could put the patient at risk for MRONJ.

Conclusion: After evaluating the results, we concluded that the awareness among dentists should be increased by educating the dentists both prior to and after graduation from dentistry faculties.

Keywords: Bisphosphonate; Denosumab; MRONJ; Osteonecrosis

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INTRODUCTION

Since the last decade of the 20th century, bisphosphonate (BP) group drugs have been used for the prevention, or the treatment of osteoporosis in the postmenopausal period, hypercalcemia, bone-related conditions such as Paget's disease, and cancers that have the ability to metastasize into the bone.¹

Recently, antiresorptive and antiangiogenic drugs (also called Antibody-mediated anti-resorptive therapy- AMART) are also being used in addition to bisphosphonates to treat both osteoporosis and metastatic bone diseases.² Denosumab is one of the most widely used drugs among these antibodies.³

In 2009, the American Society of Oral and Maxillofacial Surgeons (AAOMS) described bisphosphonate-related osteonecrosis of the jaw (BRONJ) and modified the definition in 2014 to better distinguish this type of osteonecrosis and renamed it as 'medication-related osteonecrosis of the jaw' (MRONJ).⁴

The increased use of bisphosphonates, denosumab, and other drugs with similar side effects has caused an increase in the number of osteonecrosis cases. In 2018, it is estimated that the number of new cancer cases in Europe was 3.91 million, and the number of cancer-related deaths was 1.93 million.⁵ The most common cancers have been reported to be breast cancer, colorectal cancer, lung cancer, and prostate cancer.⁶

In parallel with the increase in the number of new cancer cases, the prescription rates of bisphosphonates, denosumab, and similar drugs are also expected to increase. Thus, the physicians who prescribe these drugs and the dentists should have the required information about the indications of these drugs, their mechanisms of action, and the complications that may occur. The aim of this study was to evaluate the knowledge and approach of dentists, who are registered to the Ankara Chamber of Dentists or are working as academicians in the dentistry faculties in Ankara, to patients with MRONJ.

MATERIAL AND METHODS

This is a cross-sectional study based on web-based surveys (Survey Monkey link has been used) and face-to-face interviews conducted over a period of one month. While some of the clinicians participat-

ed by e-mail, others were interviewed face-to-face. Participation was on a voluntary basis. The study was approved by the Gazi University Ethics Review Board (03.02.2016/03) and was supported by Gazi University Scientific Research Projects Unit (03/2016-04). A questionnaire was sent to-through e-mail to 1400 dentists, who were registered to the Ankara Chamber of Dentists' e-mail list.

130 dentists participated in the online questionnaire, while 173 of them were interviewed. Participants were not compensated in any way. Incomplete responders were not included in the study. The clinicians who were interviewed face-to-face were working as academicians at Ankara University, Başkent University, or Gazi University Faculty of Dentistry.

The survey was divided into four main sections as participants' knowledge of BP, denosumab, and other drugs with similar side effects, general information and treatment about the MRONJ, scenario cases about their approach to patients using BP or denosumab, demography, and source of participants' information about the MRONJ. The answers were evaluated according to the AAOMS guidelines. The first section included 10 key questions aiming to elicit the general information of the participants about the MRONJ, its frequency and the specific clinics that the MRONJ patients were referred to. The second section included scenario cases about dentists' approach to patients using BP or denosumab and were given hypothetical cases regarding surgical intervention applied to these patients. The third section about demography involved the gender, age, the area of expertise (general practitioner, specialist, academician, research assistant, doctor and of the participants and the institution they worked for were asked. In the fourth section, the participants were asked about their sources of information (dental education, scientific meetings, journals, books or internet), and the time when they first heard about the MRONJ).

Statistical Analysis: The SPSS V.22 program was used for statistical analysis. The answers between these subgroups were compared using the Chi-square test. Fisher exact and Pearson chi-square tests were performed. A value of $p < 0.05$ was accepted as statistically significant.

RESULTS

The study included 303 participants (87 general practitioners, 73 PhD students, 86 research assistants, 28 specialist/PhD graduate, 4 lecturer and 25 faculty member). The specialty of participants was shown in Table 1.

The results of this study showed that the majority of the 303 clinicians who responded to the questionnaire (94.1%) knew that the use of BP caused osteonecrosis in the jaws. In addition, the awareness of the clinicians regarding osteonecrosis was significantly raised in 2006-2010 (28.1%) and 2010-2014 (47.2%) compared to earlier years.

The majority of the general practitioners (68.2%), PhD students (90.4%), and research assistants (91.8%) who participated in the questionnaire stated that they heard about this subject for the first time during the dental education. On the other hand, specialists/PhD graduates (69.6%), lecturers (75.0%), and faculty members (82.6%) indicated that they heard the term osteonecrosis for the first time, not during their dental education, but they learned through activities such as congresses, seminars, and symposiums.

The response of the clinicians about the indications for oral bisphosphonate (OBP) use was mostly osteoporosis (84.8%), and the correct response rate was statistically higher in female practitioners than in males (F:89.9%; M:%77.4) (Table 2).

Despite the high percentage of correct answers about indications for oral bisphosphonate use, the percentage of a correct response from the clinicians about the intravenous (IV) BP indications was low. Clinicians mostly chose the "bone metastases associated with the skeletal system" option (67.7%) as the answer to the question about the indication for IV bisphosphonate use. Other answers were 'multiple myeloma' (37.0%), 'hypercalcemia in the malignancy cases' (35.3%), and 'breast cancer' (30.4%) (Table 3).

25.4% of the surveyed clinicians correctly answered the question about the duration of the exposed bone or fistula in the maxillofacial region conclude as osteonecrosis 'In a patient using bisphosphonate or denosumab. Compared to general practitioners, the academicians were statistically more accurate in giving the correct answer to this question. However, similar percentages have been obtained when comparing the ratio of correct answers between the

Table 1. Participants' fields of dentistry

	Number	Percentage(%)
Oral and Maxillofacial Surgery	43	19.9
Oral and Maxillofacial Radiology	6	2.8
Pediatric Dentistry	43	19.9
Endodontics	19	8.8
Orthodontics	21	9.7
Periodontology	31	14.3
Prosthodontics	32	14.8
Restorative Dental Treatments	20	9.2
Periodontology and Prosthodontics	1	0.4
Toplam (N)	216	100.0

Table 2. Distribution of the answers about OBP indications.

	Number	Percentage (%) (ratio)	Percentage in Total Answers (%)
Osteoporosis	257	84.8 (257/303)	51.6 (257/498)
Osteopenia	54	17.8 (54/303)	10.8 (54/498)
Paget's Disease	112	37.0 (112/303)	22.5 (112/498)
Osteogenesis Imperfecta	46	15.2 (46/303)	9.2 (46/498)
No idea	29	9.6 (29/303)	5.8 (29/498)
Total (N)	498	100.0	100.0 (498/498)

* Multiple answers could be marked in this question, therefore, N = 498. The first column (%) represents the percentage in N = 303 people. The second column (%) shows the percentage in N = 498 answers.

Table 3. Distribution of the answers about IV BP indications.

	Number	Percentage (%) (ratio)	Percentage in Total Answers (%)*
Bone metastases associated with the skeletal system	205	67.7 (205/303)	29.5 (205/695)
Hypercalcemia in malignant cases	107	35.3 (107/303)	15.4 (107/695)
Breast cancer	92	30.4 (92/303)	13.2 (92/695)
Lung cancer	50	16.5 (50/303)	7.2 (50/695)
Prostate cancer	75	24.8 (75/303)	10.8 (75/695)
Multiple myeloma	112	37.0 (112/303)	16.1 (112/695)
No idea	54	17.8 (54/303)	7.8 (54/695)
Total (N)	695	-	100.0 (695/695)

* Multiple answers could be marked in this question, therefore, N = 695. The first column (%) represents the percentage in N = 303 people. The second column (%) shows the percentage in N = 695 answers.

general practitioners and faculty members. When specialists from different fields were compared, the clinicians working on oral and maxillofacial surgery gave significantly more (60.5%) correct answers than the other specialists.

Only 7.9% of clinicians had accurate information about the treatment approaches that should be avoided when treating patients using BP, and more than half of the participants (55.1%) had partial knowledge of the subject. The clinicians under 36 years of age gave the highest percentage of the correct answer.

The most common answers to the question about preferred department to refer the patients using BP or denosumab were 'Radiation Oncology' (56.8%), 'Orthopedics' (26.7%), and 'Internal Diseases' (23.4%), while 'Pediatrics' (1.3%), 'Dermatology' (2.0%), and 'ENT (ear-nose-throat)' (2.6%) were the least preferred departments.

When the answers given to the case study questions were evaluated, it was seen that most of the clinicians felt inadequate to apply any treatment to such patients and tend to refer these patients to the maxillofacial surgeons.

Our survey results show that very few (27.7%) of the clinicians had detailed information about the CTX (*C-telopeptide*) test and more than half of them (52.5%) avoided giving an opinion on this subject (Table 4).

In this survey, participants were also asked about MRONJ cases that are at clinical stages 0 and 3. Overall, it was observed that clinicians selected the wrong treatment options who exhibit pain, but do not have a significant etiological factor that can be observed by the clinicians. However, in the presence of an etiological factor in the mouth, such as pain and fistula, they preferred the option of referring patients to the Department of Oral and Maxillofacial Surgery. Surgeons gave the highest rate of correct answers compared to other groups (16.3% -27.9%).

In the case study questions regarding the patients who applied for implant treatment, the rate of referral to the Department of Oral and Maxillofacial Surgery was significantly decreased compared to previous scenario questions. The percentage of the correct answer for the treatment of these patients was also found to be slightly higher than other scenario questions.

Table 4. Distribution of the answers to the case study question about which test would be evaluated before planning tooth extraction in a patient using OBP

	Number	Percentage (%)
Ostase (Bone Alkaline Phosphatase) test	42	13.9
Osteocalcin test	7	2.3
OH-Pro (Hydroxy Proline) test	5	1.7
NTX test	6	2.6
CTX test	84	27.7
No idea	159	52.5
Total (N)	303	100.0

DISCUSSION

The osteonecrosis in the jaw bones due to bisphosphonate use was first observed in 2003 by Marx *et al.* and the universal definition of bisphosphonate osteonecrosis in the report published by AAOMS in 2009.^{1,4,7} It is clear that the recognition of osteonecrosis among dentists is directly related to the definition of the term osteonecrosis in 2009 and the importance of teaching this subject during dentistry education increased after that year. The statistical results obtained in this study confirm this association. The present study also showed that the widespread use of the internet and printed publications also contributed to the increase in the knowledge of clinicians about the subject.

Clinicians mostly choose the “skeletal system-related bone metastases” answer for the question about the indication for the use of IV bisphosphonates. 2012 data from the International Cancer Research Center shows that the most common types of cancer in Turkey are lung, breast, and prostate cancers.⁵ These types of cancer have a high rate of bone metastasis, thus the reason that the answer to this question was “skeletal system-related bone metastases” may be related to that.

The clinicians working in the field of Oral and Maxillofacial Surgery gave more correct answers than the other divisions and general practitioners about IV BP indications. Although the statistical results of the clinicians working in the “Oral Diagnosis and Radiology” and in the surgical branch were similar, it is hard to compare their results with other branches because the number of radiologists participating in the survey was very low (6 clinicians).

The low number of the Oral Diagnosis and Radiology clinicians in our survey also makes it difficult for statistical ratios to be representative of all radiologists, but it is known that the radiologists and surgeons more frequently encounter with this group of patients compared to other specialists and general practitioners.

In this study, the rate of correct answers given to the questions about the frequency of using zoledronate and ibandronate was found to be quite low. The highest percentage of the correct answer for the questions regarding the frequency of zoledronate

use (16.3%) and the frequency of ibandronate use (14.0%) was observed in the surgeon subgroup. Generally, the reason for the low rate of correct response may be attributed to the lack of practice of dentists on the subject, because dentists are not authorized to prescribe, dose, or administer BP to patients. Furthermore, due to the different application frequencies for different drugs in the AAOMS guideline on the use of BPs, it can be suggested that the clinicians who responded to the questions about the frequency of drug use were confused and performed poorly.

The rate of correct answers to the question about the duration of the exposure of the bone or fistula that is required to diagnose osteonecrosis was higher among surgeons compared to others. This can be attributed to the fact that the surgeons encounter this group of patients more than the other specialists from other departments.

Previous studies showed that the incidence of MRONJ was higher in the mandible than maxilla.^{8,9} In our study, the majority of the clinicians (74.6%) agreed that the MRONJ of the jaws was most frequently seen in the mandible. However, the percentage of the correct answer was observed to decrease as the age of the group increased, and the rate of the correct answer by clinicians over 50 years of age was significantly lower compared to clinicians under 50 years of age. When the results were evaluated with respect to the specialties of the clinicians, it was observed that the dentists working in the Department of Prosthetic Dentistry showed the lowest correct response rate (56.3%).

The rate of correct response among the clinicians under the age of 36 was higher regarding the question about the types of treatments that should be avoided in patients who are taking bisphosphonates. The younger dentists, between the ages of 25-35, have learned about MRONJ as part of the curriculum in the Dental School (the topic has been introduced into the curriculum in Turkey in the 2006-2007 academic year), thus they have more up-to-date information and the percentage of correct answers was higher for this group compared to the other age groups. The rate of correct answers was also higher than the group who were 20-25 years of age, probably because of the fact that they are more experienced than this group.

In a study conducted by Yoo *et al.*, the rate of people who knew the relationship between bisphosphonate use and osteonecrosis was found to be 56%, it was reported that the percentage of clinicians recording the use of bisphosphonates in the anamnesis forms was only 31.4%. In the cross-sectional analysis, it was observed that the rate of awareness of the AAOMS guidelines was very low. When compared in terms of clinical experience, it was reported that clinicians who have less than 5 years of experience are more knowledgeable than the clinicians who have more than 5 years of experience.¹⁰ In addition, it was shown that the clinicians who are more knowledgeable on this subject were the ones who graduated after 2004.¹⁰ In parallel with these results, in our survey, it was found that the rate of correct answers was higher among dentists who had graduated after 2003 and has some clinical experience, compared to the other age groups.

In a study conducted by El Osta *et al.* involved physicians from different departments and 85/136 of the participating physicians stated that they applied bisphosphonate therapy, but their level of awareness about the BRONJ complications that these drugs cause was found to be inadequate.¹¹

Before applying any invasive procedures to patients using BP, their clinicians should perform a consultation regarding medication cut-off or dose adjustment and act according to this consultation response. Although there are no published surveys similar to El Osta's work involving medical doctors in Turkey, it would be important that the dentists write about the consultation in a descriptive and detailed manner, considering the likelihood that there is low awareness about MRONJ among medical doctors.

The most common preferred department to refer the patients using BP or denosumab were 'Radiation Oncology' (56.8%), 'Orthopedics' (26.7%), and 'Internal Diseases' (23.4%). The name of Radiation Therapy Chair which was founded in 1933, with the aim of apply radiotherapy for the first time has been changed to the Department of Radiation Oncology after the establishment and operation of the 'Radiation Oncology Association' in 1993. The questionnaire participating doctors likely mix up the Department of Radiation Oncology with the Department of Oncology which is actually a subspecialty of the Internal Medicine Department. And that's, why

is thinking that percentage of this choice, is higher than expected.

Yoo *et al.* also reported that the most knowledgeable group was Oral, Dental and Maxillofacial Surgeons, which is in line with the results obtained in the present study.¹⁰

This study includes responses from a group of dentists residing in Ankara, not medical doctors. However, our data suggest that whether it is for osteoporosis or other medical reasons, and whether it is administered orally or parenterally, dentists generally do not have sufficient knowledge on the use of BPs. Although oral and maxillofacial surgeons, who practice the most radical treatments in the field of dentistry, encounter patients who have symptoms described in the scenario questions of the survey more frequently, it was observed that they also seem to have insufficient knowledge.

A study by McLeod *et al.* aimed to determine how the dentists working in these departments approach patients who use BPs or have used it in the past and need a tooth extraction and to review current guidelines for the treatment of these patients. 8% of the responding units reported that they had established protocols for the treatment of these patients. These protocols, which were used to prevent bisphosphonate osteonecrosis, were reported to include chlorhexidine mouthwash, and pre- and postoperative antibiotic use.¹² The results of this study suggest that installing a treatment protocol in hospitals for MRONJ may increase the awareness of the clinicians.

As currently done in many developed countries, making continuing education obligatory will also enable clinicians to update their knowledge. In addition, dentistry and other training related to this subject should be given in more detail at the universities, special issues in the relevant professional journals may be issued and congresses and symposia in the fields of medicine, dentistry, and pharmacy may be organized, which would increase the awareness of clinicians about the subject.

The medical profession brings the responsibility of lifelong learning with it, and clinicians should not ignore it. Medicine is an active area where new therapies, drugs, and applications are constantly

introduced, and the clinician's job is to follow these developments and update their knowledge.

In parallel with the rapid increase in global cancer cases, the rate of prescription of drugs used for the treatment of these patients is increasing, which may lead to osteonecrosis in the jaws. Therefore, it is extremely important to carry out further studies on this subject.

Limitations of this study: A questionnaire was sent to the e-mail addresses of 1400 dentists registered to the Ankara Chamber of Dentists (ADO) through the chamber's e-mail list and more than 80% of mail didn't reply. Incomplete responders were not included in the study. The clinicians who were interviewed face-to-face were working as academicians at Ankara University, Gazi University, Baskent University Faculty of Dentistry.

CONCLUSION

In order to determine the level of knowledge of clinicians in Turkey and to raise awareness among them about the factors causing MRONJ, its clinical manifestations, and the treatment of MRONJ patients, it will be helpful to survey clinicians providing services in cities other than Ankara and to make more comprehensive studies including medical doctors and pharmacists. In addition, more studies on this subject should be performed worldwide and standardization regarding MRONJ treatment in this area should be ensured.

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