

Physicians' awareness of bisphosphonates-related osteonecrosis of the jaw

Maha A. Al-Mohaya, MS, DMS, Hesham I. Al-Khashan, SBFM, ABFM, Adel M. Mishriky, MD, PhD, Lubna M. Al-Otaibi, MS, PhD.

ABSTRACT

الأهداف: تقييم مدى وعي ومعرفة أطباء الأسنان بشكل خاص، والأطباء بشكل عام حول تنخر عظم الفك الناتج عن تناول عقار البايفوسفونيت (bisphosphonate).

الطريقة: أُجريت هذه الدراسة المقطعية الوصفية في قسم الأسنان، مستشفى القوات المسلحة بالرياض، المملكة العربية السعودية، واستمرت خلال الفترة من يونيو إلى سبتمبر 2010م. لقد قمنا بجمع البيانات التي نحتاجها للدراسة من خلال توزيع أوراق الاستبيان الذاتية التعبئة على عينة من الأطباء وأطباء الأسنان في المستشفى.

النتائج: لقد قمنا بجمع ما مجموعه 222 من الإجابات الكاملة والصالحة (معدل الإجابة: 82.2%). أشارت نتائج الدراسة إلى أن أقل من ثلث المشاركين (31.5%) قد كانوا على دراية بمشكلة تنخر عظم الفك، فيما لجأ أكثر من نصفهم تقريباً إلى عقار البايفوسفونيت لعلاج المرضى. ولم يصل أي من الأطباء الذين شاركوا في الدراسة إلى الإجابة الصحيحة على الأسئلة الأربعة المتعلقة بالمعرفة. وقد كان هناك علاقة كبيرة من الناحية الإحصائية بين مستوى المعرفة وكلاً من: المؤهل ($p=0.019$)، وسنوات الخبرة ($p=0.002$)، والتخصص ($p=0.034$).

خاتمة: لقد وجدنا أنه لم يكن للأطباء وأطباء الأسنان المعرفة والوعي الكافي حول مشكلة تنخر عظم الفك الناتج عن عقار البايفوسفونيت، بالرغم من أن الكثير منهم قد قاموا بوصف هذا العقار لمرضاهم. ولذلك فإنه يجب التدخل من أجل رفع مستوى المعرفة والوعي التي يحتاجها الأطباء لمواجهة هذه المشكلة.

Objectives: To assess the awareness and knowledge of physicians and dentists regarding bisphosphonates related osteonecrosis of the jaw (BRONJ).

Methods: A cross-sectional descriptive study was carried out in the Department of Dentistry, Riyadh Military Hospital, Kingdom of Saudi Arabia from June to September 2010. Data were collected through a self-administered questionnaire distributed among a sample of physicians and dentists at the hospital.

Results: A total of 222 valid completed responses were obtained (response rate: 82.2%). Less than one-third of the participants (31.5%) were aware of osteonecrosis of the jaw, while slightly more than half of them were treating patients with bisphosphonates (BP). None of the physicians had a correct response in all 4 knowledge questions. There were statistically significant associations between knowledge and qualification ($p=0.019$), years of experience ($p=0.002$), and specialty ($p=0.034$).

Conclusions: We found that physicians and dentists have low awareness and deficient knowledge regarding BRONJ, although most of them do prescribe BP to their patients. Therefore, intervention to raise awareness and knowledge among healthcare providers is needed.

Saudi Med J 2011; Vol. 32 (8): 830-835

From the Departments of Dentistry, Oral Medicine (Al-Mohaya, Al-Otaibi), Family and Community Medicine (Al-Khashan, Mishriky), Riyadh Military Hospital, Riyadh, Kingdom of Saudi Arabia, and the Department of Community, Environmental, and Occupational Medicine (Mishriky), Faculty of Medicine, Suez Canal University, Egypt.

Received 8th May 2011. Accepted 20th June 2011.

Address correspondence and reprint request to: Dr. Maha A. Al-Mohaya, Head of Oral Medicine, Medically Compromised, and Research Clinic, Department of Dentistry, Riyadh Military Hospital, PO Box 7897, Riyadh 11159, Kingdom of Saudi Arabia. Tel. +966 555051452. Fax. +966 (1) 4777714 Ext. 23312. E-mail: mmohaya@hotmail.com / maalmohaya@rmh.med.sa

Bisphosphonates (BP) are a class of drugs used successfully to treat osteoporosis, Paget's disease of bone and other metabolic bone diseases, multiple myeloma, and skeletal events associated with metastatic neoplasms. Their primary mechanism of action is inhibition of osteoclastic resorption of bone.¹ The efficacy of these agents in treating and preventing the significant skeletal complications associated with these conditions has had a major positive impact for

patients, and is responsible for their widespread use in medicine.²⁻⁴ Despite these benefits, a significant complication in a subset of patients receiving these drugs has recently emerged, and has been named "osteonecrosis of the jaw" (ONJ). In 2003-2004, the first reports of patients who developed necrosis of the jawbones while taking BPs appeared in the literature. Most patients were on this drug for treatment of cancer, and some for osteoporosis.⁵⁻⁷ Since then, hundreds of cases worldwide have been identified, and the number of these cases continues to grow. Based on the clear association between BP therapy, especially nitrogen-containing forms and jaw necrosis that has been established in numerous retrospective studies, the American Association of Oral and Maxillofacial Surgeons (AAOMS) has decided to adopt the term "BRONJ" (bisphosphonate-related osteonecrosis of the jaw) for this entity. It has been defined as "the presence of exposed bone that [does] not heal within 8 weeks with no history of craniofacial radiation".⁸ The exact mechanism for the development of BRONJ is not completely understood. The current hypothesis focuses on severe suppression of bone turnover, together with the toxic effect on soft tissues including anti-angiogenesis, coupled with the unique conditions affecting the jaws, and not other bones. These conditions include the separation of the jaw bones from the oral environment by a very thin mucosa, very vulnerable to be breached even with simple physiologic activities, such as mastication, the tremendous numbers of bacteria in the oral cavity often involved in infection through either the periodontal ligament or the pulp, and the high turnover rate of the jawbones. Additionally, the dento-alveolar interventions such as extractions, periodontal surgeries, and apicoectomies, in which bone is exposed to a bacteria-rich environment are quite common.^{9,10} The incidence and prevalence of ONJ is largely unknown. However, most of the studies have reported a low prevalence of ONJ.¹¹⁻¹³ A recent systematic review has demonstrated an overall weighted prevalence of ONJ in a sample of 39,124 patients to be 6.1%.¹⁰ We believe that awareness and knowledge of this newly documented complication among both physicians and patients are important determinants of early recognition, diagnosis and management, which will all contribute to determine its incidence and sequels. The primary purpose of the present study was to assess the awareness and knowledge regarding BRONJ in a

sample of physicians and dentists in Riyadh Military Hospital (RMH) in the Kingdom of Saudi Arabia (KSA) using a self-administered questionnaire. We also sought to examine, whether awareness and knowledge vary by specialty and qualifications.

Methods. A cross-sectional descriptive design was used. This study was carried out in the Department of Dentistry, RMH, and its affiliated primary health care centers. The hospital and centers provide health services at all 3 levels of care to military personnel and their dependents.

Study sample. All physicians working in the hospital setting during the time of the study from June to September 2010 were eligible for inclusion in the sample (excluding interns and medical trainees). The eligibility criteria were: having a work experience of at least one year in the setting, and working in a department where BP medication may be used. These were the Departments of Endocrinology, Oncology, Rheumatology, Maxillo-facial, Dental, Orthopedics, Internal Medicine, and Family Medicine. The total number of eligible physicians in these departments was approximately 500. The sample size was calculated to estimate an awareness rate of 50% or higher, with a 10% standard error, and at a 95% confidence level. Using the sample size equation for a single proportion with finite population correction (Epi-Info 6.04), the required sample size was found to be 217 participants. This was increased to 270 to compensate for a dropout rate of 20%. This sample size was divided proportionately among the aforementioned departments according to their physicians' workforce.

Data collection tool. The data were collected through a self-administered questionnaire designed by the researcher and based on a review of pertinent literature.^{1,8-10} It was thoroughly revised by experts in oral medicine, endocrinology, internal medicine, and epidemiology. The questionnaire included a part for personal data as job position, qualification, and experience. The second part asked on awareness of the condition of ONJ, and the use of BP in practice, with related ONJ as a possible complication. The third part included 4 multiple choice questions to assess physician's knowledge regarding ONJ definition, clinical picture, proper management, and when to stop BP. The scores of correct answers were simply summed up to give a maximum knowledge score of 4 points.

Pilot study. A pilot study was carried out in the same study setting to assess tool clarity, and the feasibility of the study. Based on the pilot results, modifications were carried out on the questionnaire, with omission of open-ended questions, and re-arrangement of the tool sections. The pilot sample was not included in the main study sample.

Disclosure. The authors have no conflict of interests and this work was not supported or funded by any drug company.

Fieldwork. Upon securing official permissions to conduct the study, and pilot testing the tool, the data collection process was started. A sampling frame of all eligible physicians was constructed. The questionnaires were distributed to the selected departments to be filled-out by physicians, and returned anonymously through the department secretary of the research center. The questionnaire was self-explanatory, with a cover letter indicating the purpose of the study, and asking for cooperation. This process took approximately 3 weeks during the month of June 2010.

The research proposal was approved by the research committee of the hospital. The questionnaire was anonymous, and respondents were free to participate or refuse without giving any reason, and with no consequences. They were reassured that the information obtained would be used only for research purposes. The study procedures would not entail any harmful effects on the participants.

Data entry and statistical analysis were carried out using the Statistical Package for Social Sciences version 14.0 (IBM SPSS Inc, Chicago, IL, USA). Quantitative continuous data were compared using the non-parametric Kruskal-Wallis and Mann-Whitney tests, since the assumptions of normal distribution of the data and equal variance were not fulfilled. Statistical significance was considered at $p < 0.05$.

Results. A total of 222 valid completed responses were obtained (response rate 82.2%). They were mostly registrars (32.9%), and consultants (25.7%) as shown in Table 1. More than two-thirds had a post-graduate degree, and work experience of 10 years or more. Approximately half of the sample was from the Family Medicine Department, and 17.6% were from the Dental Department. According to the study results, only less than one-third of the participants (31.5%) were aware of ONJ, while slightly more than half of them were treating patients with BP (Table 2). In most cases, the main indication for BP was osteoporosis, in oral type, and with no adjuvant medications. More than half of the physicians never examined the patient's mouth before, during, or after BP therapy, and never recommended pre-treatment dental screening. It was also found that 22.2% of the physicians noticed bone necrosis of the jaw among their BP-treated patients (Table 2). Concerning physicians' knowledge on ONJ, it was very deficient as shown in Table 3. The percentages of correct knowledge ranged between 2.7% for ONJ clinical picture, and 45.9% for proper action if ONJ is suspected in BP-treated patient. Table 3 also demonstrates that none of the physicians had a correct response for all 4 knowledge questions, whereas 29.7% had incorrectly answered all 4 questions. When the relation between knowledge

and physicians' characteristics was examined (Table 4), statistically significant associations were revealed with qualification ($p=0.019$), experience years ($p=0.002$), and specialty ($p=0.034$). Physicians with doctorate degree had the highest knowledge score, while those with post-graduate diploma had the lowest score. The knowledge score had also an increasing trend with the years of experience. As for specialty, endocrinology, and oncology had the highest scores, whereas internal medicine, orthopedics, and maxillo-facial surgery had the lowest scores. The relation between awareness of ONJ and practice of treating patients with BP on one hand, and physicians' knowledge on the other hand turned out to be statistically significant (Table 5). It was evident that the knowledge scores of physicians who were aware of ONJ, and who were treating patients with BP were higher.

Discussion. Our study findings revealed a low level of awareness of ONJ among respondent physicians and dentists, with less than one-third of them having limited information regarding this condition. Meanwhile, almost half of these respondents were treating patients with BP, indicating that a certain percentage of these physicians were prescribing BP without knowledge of its potential side effect concerning the occurrence of ONJ. Such findings might entail serious harmful effects

Table 1 - Description of the study sample (n=222).

Variables	Frequency	(%)
Job position		
Consultant	57	(25.7)
Senior registrar	40	(18.0)
Registrar	73	(32.9)
Resident	52	(23.4)
Highest qualification		
Doctorate	48	(21.6)
Master	75	(33.8)
Postgraduate diploma	33	(14.9)
Bachelor	66	(29.7)
Experience, years		
less than 5	45	(20.3)
5-less than 10	36	(16.2)
10-less than 15	66	(29.7)
15+	75	(33.8)
Specialty		
Endocrinology	6	(2.7)
Oncology	5	(2.3)
Rheumatology	8	(3.6)
Maxillo-facial	5	(2.3)
Dental	39	(17.6)
Orthopedics	25	(11.3)
Internal Medicine	25	(11.3)
Family Medicine	109	(49.1)
Level of care		
Primary Health Care	113	(50.9)
Hospital	109	(49.1)

Table 2 - Awareness of osteonecrosis of the jaw and practices related to use of bisphosphonates (BP) as reported by doctors who used it (n=117).

Variables	Frequency	(%)
Aware of osteonecrosis of the jaw (n=222)	70	(31.5)
Treat patients with BP; (n=222)	117	(52.7)
<i>Number of patients on BP attended per month</i>		
1-5	87	(74.4)
6-10	19	(16.2)
11+	11	(9.4)
<i>Indications of BP use</i>		
Cancer	2	(1.7)
Osteoporosis	107	(91.5)
Other	8	(6.8)
<i>Type of BP used</i>		
Intravenous	1	(0.9)
Oral	108	(92.3)
Other	8	(6.8)
<i>Other adjuvant medications with BP</i>		
None	102	(87.2)
Corticosteroids	10	(8.5)
Chemotherapy	5	(4.3)
<i>Examine patient's mouth before starting BP therapy</i>		
Never	67	(57.3)
Occasionally	36	(30.8)
Usually	14	(12.0)
<i>Examine patient's mouth during BP therapy</i>		
Never	67	(57.3)
Occasionally	38	(32.5)
Usually	12	(10.3)
<i>Examine patient's mouth after BP therapy</i>		
Never	69	(59.0)
Occasionally	37	(31.6)
Usually	11	(9.4)
<i>Recommend dental screening to patients prior to BP therapy</i>		
Never	76	(65.0)
Occasionally	36	(30.8)
Usually	5	(4.3)
<i>Have ever noticed exposed necrotic bone of the jaw among patients</i>		
No	73	(62.4)
Yes	26	(22.2)
Do not know	18	(15.4)
<i>Number of patients seen with this condition, n=26</i>		
less than 3	24	(92.3)
5-9	2	(7.7)

Table 3 - Correct knowledge of osteonecrosis of the jaw (ONJ) among doctors in the study sample (n=222).

Knowledge	Frequency	(%)
<i>Correct knowledge of ONJ</i>		
Definition	40	18.0
Clinical picture	6	2.7
Proper action if suspected	102	45.9
Stopping BP therapy	77	34.7
<i>Total correct answers (maximum=4)</i>		
0	66	29.7
1	102	45.9
2	39	17.6
3	15	6.8

Table 4 - Relation between doctors' scores knowledge of osteonecrosis of the jaw and their personal and work characteristics.

Characteristics	Knowledge score Mean \pm standard deviation	N	Kruskall Wallis test	P-value		
<i>Job position</i>						
Consultant	1.16 \pm 0.82	57	3.977	0.264		
Senior registrar	0.90 \pm 0.81	40				
Registrar	1.04 \pm 0.90	73				
Resident	0.90 \pm 0.89	52				
<i>Highest qualification</i>						
Doctorate	1.29 \pm 0.80	48	9.935	0.019*		
Master	0.99 \pm 0.89	75				
Postgraduate diploma	0.73 \pm 0.67	33				
Bachelor	0.98 \pm 0.92	66				
<i>Experience years</i>						
<5	0.78 \pm 0.80	45	15.010	0.002*		
5-<10	0.86 \pm 0.87	36				
10-<15	0.91 \pm 0.80	66				
15+	1.32 \pm 0.89	75				
<i>Specialty</i>						
Endocrinology	1.83 \pm 0.41	6	15.161	0.034*		
Oncology	1.40 \pm 0.55	5				
Rheumatology	1.13 \pm 0.99	8				
Family Medicine	1.06 \pm 0.92	109				
Dental	1.05 \pm 0.92	39				
Internal Medicine	0.84 \pm 0.80	25				
Orthopedics	0.72 \pm 0.46	25				
Maxillo-facial	0.40 \pm 0.89	5				
<i>Level of care</i>						
Primary Health Care	0.96 \pm 0.81	113			0.395 [†]	0.530
Hospital	1.06 \pm 0.92	109				

*Statistically significant at $p < 0.05$, [†]Mann-Whitney test**Table 5** - Relation between doctors' scores knowledge of osteonecrosis of the jaw (ONJ) and their awareness and practice.

Variables	Knowledge score Mean \pm standard deviation	N	Mann-Whitney test	P-value
<i>Aware of ONJ</i>				
No	0.84 \pm 0.76	152	18.469	<0.001*
Yes	1.40 \pm 0.95	70		
<i>Treat patients with bisphosphonates</i>				
No	0.88 \pm 0.79	105	4.224	0.040*
Yes	1.14 \pm 0.91	117		

Statistically significant at $p < 0.05$ *

that could be prevented, if the provider was aware of it. In this respect, Vassiliou et al¹⁴ emphasized that given the seriousness of ONJ, and the importance of early detection and effective management, physicians and dentists must have good knowledge regarding the condition. Moreover, they should inform their patients on BP regarding the risk of developing ONJ, and its predisposing factors.^{15,16} It is worth mentioning that patient's awareness is equally important. A recent study¹⁷ has demonstrated that people taking BPs may be unfamiliar with the drug, and its possible adverse oral side effects.

Going in more depth beyond just awareness, the present study assessed physicians and dentists' factual knowledge in 4 areas of ONJ, namely: definition; clinical picture; proper action in suspected cases; and when to stop BP. The knowledge of the clinical picture and oral manifestations of ONJ was the lowest. The low awareness and deficient knowledge revealed among our study participants might have more than one explanation. Firstly, although the literature abounds with reports addressing the problem, there are still many knowledge gaps related to it. For instance, there is no uniform definition of the condition, or its etiology and pathophysiology.¹⁸ In fact, less than one-fifth of our sample had limited knowledge on the definition of ONJ. Secondly, in almost all cases in the present study, the indication for prescribing BP was osteoporosis with use of its oral form, which is known to have a lower risk for ONJ.^{19,20} However, a recent study²¹ revealed a strong association between the risk of ONJ and oral BP. Thirdly, the use of adjuvant medications as chemotherapy, or cortisone was minimal in the present study sample, which further decreases the chance of developing ONJ,²² and consequently would make physicians less concerned of this complication.

The deficient knowledge regarding ONJ demonstrated among the current study participants was reflected on their practice. Thus, more than half of the practitioners who were prescribing BP to their patients never practiced any of the preventive measures that would mitigate the occurrence of ONJ before, during, or after initiating BP therapy. Such deficient practice can jeopardize the safety of their patients, and expose them to serious problems that can have detrimental effects on their quality of life.²³ This is of particular importance, since prevention and early intervention proved to be successful in avoiding the occurrence and sequels of ONJ.^{24,25}

In the current study, the knowledge scores were higher among physicians who were treating patients with BP. This reflects the effect of practice as a stimulus to seek information. Other factors that had significant relations with our participants' knowledge were their qualification, years of experience, and specialty. As expected, higher qualification and longer years of experience were associated with better knowledge scores. Also, endocrinologists and oncologists had the highest scores, but paradoxically dentists, and maxillo-facial surgeons had low scores. The high scores among oncologists are certainly due to the higher incidence of ONJ among their patients, which ranges from 0.94-18.6% in cancer patients on intravenous BP,²⁶ compared to less than 1 per 100,000 in osteoporotic patients on oral BP.²⁷ On the other hand, the low scores among dentists and maxillo-facial surgeons need some explanation. The

finding is quite alarming, since oral health is considered the key for prevention of ONJ among patients on BP.²⁸ Furthermore, the risk factors for development of ONJ among patients on BP include suppuration,²¹ dental extraction,²⁹ and other dental surgical procedures.³⁰ Therefore, the awareness of dentists and maxillo-facial surgeons regarding ONJ is critical in saving patients on BP from this dreadful complication. Hence, Weitzman et al³¹ recommended that before the start of BP therapy, patients should receive dental examination, along with regular dental check ups during therapy.

According to our study findings, approximately one-fourth of those who prescribed BP reported having noticed bone necrosis of the jaw among their BP-treated patients. In other words, at least 25 cases of ONJ have been encountered in this setting. This is considered a very high figure given that most of the cases were osteoporotic patients treated with oral BP. With a rate of 1 per 60,000 as reported by Bolland et al³² in osteoporotic patients on oral BP, these 25 cases would occur in more than one million patients. Therefore, the rate is certainly an over-estimation that could be due to lack of knowledge among physicians in the present study. Nonetheless, it implies the possible presence of the problem of ONJ that needs further investigation to estimate its real magnitude in the study setting.

The study findings lead to the conclusion that physicians and dentists have low awareness and deficient knowledge regarding ONJ, although many of them do prescribe BP to their patients. The deficiency is more evident among dentists and maxillo-facial surgeons, which may be related to the insufficient updated educational programs. The study findings should be interpreted, taking into consideration its limitations, such as the use of a non-probability convenience sample, and of self-reporting. In-service training is recommended to improve their knowledge. Further research is needed to determine the magnitude of the problem in KSA to fill this gap. Moreover, intervention to raise awareness and knowledge among healthcare providers is needed. Educational efforts should be targeted to assist physicians in risk assessment, recognition, management, and implementing a preventive strategy. Thorough medical and drug history should be obtained carefully for all patients. Patients with BP should be informed of the benefits and risks of this medication, including the risk of ONJ.

It is highly recommended that patients who have been scheduled to receive BP, especially intravenous forms should undergo dental screening before the commencement of treatment. During and after therapy, doctors are encouraged to do regular oral examination, which might help in the early detection of ONJ lesions, and facilitate their management.

Acknowledgment. The authors gratefully acknowledge the contributions of Dr. Najwa Ibrahim, Department of Clinical Pharmacology, and Dr. Ali Al-Zahrani, Department of Oncology, Riyadh Military Hospital, Riyadh, Kingdom of Saudi Arabia.

References

- Migliorati CA, Epstein JB, Abt E, Berenson JR. Osteonecrosis of the jaw and bisphosphonates in cancer: a narrative review. *Nat Rev Endocrinol* 2011; 7: 34-42.
- Lipton A, Theriault RL, Hortobagyi GN, Simeone J, Knight RD, Mellars K, et al. Pamidronate prevents skeletal complications and is effective palliative treatment in women with breast carcinoma and osteolytic bone metastases: long term follow-up of two randomized, placebo-controlled trials. *Cancer* 2000; 88: 1082-1090.
- Berenson JR, Rosen LS, Howell A, Porter L, Coleman RE, Morley W, et al. Zoledronic acid reduces skeletal-related events in patients with osteolytic metastases. *Cancer* 2001; 91: 1191-1200.
- Saad F. Clinical benefit of zoledronic acid for the prevention of skeletal complications in advanced prostate cancer. *Clin Prostate Cancer* 2005; 4: 31-37.
- Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. *J Oral Maxillofac Surg* 2003; 61: 1115-1117.
- Migliorati CA. Bisphosphonates and oral cavity avascular bone necrosis. *J Clin Oncol* 2003; 21: 4253-4254.
- Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. *J Oral Maxillofac Surg* 2004; 62: 527-534.
- Ruggiero SL, Dodson TB, Assael LA, Landesberg R, Marx RE, Mehrotra B. American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws--2009 update. *J Oral Maxillofac Surg* 2009; 67: 2-12.
- Ruggiero SL, Woo SB. Bisphosphonate-related osteonecrosis of the jaws. *Dent Clin North Am* 2008; 52: 111-128.
- Migliorati CA, Woo SB, Hewson I, Barasch A, Elting LS, Spijkervet FK, et al. A systematic review of bisphosphonate osteonecrosis (BON) in cancer. *Support Care Cancer* 2010; 18: 1099-1106.
- Bamias A, Kastritis E, Bamia C, Mouloupoulos LA, Melakopoulos I, Bozas G, et al. Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: incidence and risk factors. *J Clin Oncol* 2005; 23: 8580-8587.
- Dimopoulos MA, Kastritis E, Anagnostopoulos A, Melakopoulos I, Gika D, Mouloupoulos LA, et al. Osteonecrosis of the jaw in patients with multiple myeloma treated with bisphosphonates: evidence of increased risk after treatment with zoledronic acid. *Haematologica* 2006; 91: 968-971.
- Hoff AO, Toth BB, Altundag K, Johnson MM, Warneke CL, Hu M, et al. Frequency and risk factors associated with osteonecrosis of the jaw in cancer patients treated with intravenous bisphosphonates. *J Bone Miner Res* 2008; 23: 826-836.
- Vassiliou V, Tselis N, Kardamakis D. Osteonecrosis of the jaws: clinicopathologic and radiologic characteristics, preventive and therapeutic strategies. *Strahlenther Onkol* 2010; 186: 367-373.
- Favia G, Pilolli GP, Maiorano E. Osteonecrosis of the jaw correlated to bisphosphonate therapy in non-oncologic patients: clinicopathological features of 24 patients. *J Rheumatol* 2009; 36: 2780-2787.
- Solomon DH, Rekedal L, Cadarette SM. Osteoporosis treatments and adverse events. *Curr Opin Rheumatol* 2009; 21: 363-368.
- Migliorati CA, Mattos K, Palazzolo MJ. How patients' lack of knowledge about oral bisphosphonates can interfere with medical and dental care. *J Am Dent Assoc* 2010; 141: 562-566.
- Silverman SL, Landesberg R. Osteonecrosis of the jaw and the role of bisphosphonates: a critical review. *Am J Med* 2009; 122 (Suppl 2): S33-S45.
- Rizzoli R, Burlet N, Cahall D, Delmas PD, Eriksen EF, Felsenberg D, et al. Osteonecrosis of the jaw and bisphosphonate treatment for osteoporosis. *Bone* 2008; 42: 841-847.
- Pazianas M, Miller P, Blumentals WA, Bernal M, Kothawala P. A review of the literature on osteonecrosis of the jaw in patients with osteoporosis treated with oral bisphosphonates: prevalence, risk factors, and clinical characteristics. *Clin Ther* 2007; 29: 1548-1558.
- Barasch A, Cunha-Cruz J, Curro FA, Hujuel P, Sung AH, Vena D, et al. Risk factors for osteonecrosis of the jaws: a case-control study from the CONDOR dental PBRN. *J Dent Res* 2011; 90: 439-444.
- Fellows JL, Rindal DB, Barasch A, Gullion CM, Rush W, Pihlstrom DJ, et al. ONJ in two dental practice-based research network regions. *J Dent Res* 2011; 90: 433-438.
- Miksad RA, Lai KC, Dodson TB, Woo SB, Treister NS, Akinyemi O, et al. Quality of life implications of bisphosphonate-associated osteonecrosis of the jaw. *Oncologist* 2011; 16: 121-132.
- Khan AA, Sandor GK, Dore E, Morrison AD, Alsahli M, Amin F, et al. Canadian consensus practice guidelines for bisphosphonate associated osteonecrosis of the jaw. *J Rheumatol* 2008; 35: 1391-1397.
- Siddiqi A, Payne AG, Zafar S. Bisphosphonate-induced osteonecrosis of the jaw: a medical enigma? *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2009; 108: 1-8.
- Vahtsevanos K, Kyrgidis A, Verrou E, Katodritou E, Triaridis S, Andreadis CG, et al. Longitudinal cohort study of risk factors in cancer patients of bisphosphonate-related osteonecrosis of the jaw. *J Clin Oncol* 2009; 27: 5356-5362.
- Khan AA, Sandor GK, Dore E, Morrison AD, Alsahli M, Amin F, et al. Bisphosphonate associated osteonecrosis of the jaw. *J Rheumatol* 2009; 36: 478-490.
- Kunchur R, Goss AN. The oral health status of patients on oral bisphosphonates for osteoporosis. *Aust Dent J* 2008; 53: 354-357.
- Hoff AO, Toth B, Hu M, Hortobagyi GN, Gagel RF. Epidemiology and risk factors for osteonecrosis of the jaw in cancer patients. *Ann N Y Acad Sci* 2011; 1218: 47-54.
- Cohen HV. Bisphosphonate-associated osteonecrosis of the jaw: patient care considerations: overview for the orthopaedic nursing healthcare professional. *Orthop Nurs* 2010; 29: 176-180.
- Weitzman R, Sauter N, Eriksen EF, Tarassoff PG, Lacerna LV, Dias R, et al. Critical review: updated recommendations for the prevention, diagnosis, and treatment of osteonecrosis of the jaw in cancer patients--May 2006. *Crit Rev Oncol Hematol* 2007; 62: 148-152.
- Bolland M, Hay D, Grey A, Reid I, Cundy T. Osteonecrosis of the jaw and bisphosphonates--putting the risk in perspective. *N Z Med J* 2006; 119: U2339.