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Perception of Medication-related Osteonecrosis of the Jaws among Iraqi Medical Specialists

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Abstract

Objective Osteonecrosis of the jaws is the adverse effect of antiresorptive and antiangiogenic agents, which is termed as medication-related osteonecrosis of the jaws (MRONJ). This complication, which is prominent and growing, is seen in the oral and maxillofacial region. This cross-sectional survey aimed to evaluate MRONJ awareness among Iraqi medical specialists.

Materials and Methods A questionnaire-based survey was performed on medical specialists practicing general surgery, urology, orthopedics, rheumatology, and oncology. The questionnaire consisted of four questions regarding drug prescription, patients' preparation before drug administration, in addition to awareness and knowledge about MRONJ.

Results Among 132 specialists, 57% did not prescribe such drugs. A significant difference existed among groups regarding dental referral, and MRONJ awareness and knowledge. The highest rates were seen in the oncologist group.

Conclusions Improvement of MRONJ perception and knowledge among medical specialists, besides implementation of dental referral, are essential in the prevention, diagnosis and treatment of MRONJ.

Keywords
- perception
- awareness
- medication-related osteonecrosis of the jaws (MRONJ)
- questionnaire
- specialists

Introduction

Antiresorptive and the antiangiogenic agents are prescribed by a wide variety of medical specialists for patients with bone metastasis, multiple myeloma, breast cancer, prostate cancer, or metabolic bone diseases like osteoporosis, osteogenesis imperfecta, Paget's disease of bone, primary hyperparathyroidism, fibrous dysplasia, and other conditions that exhibit bone fragility.[1-3] In spite of these benefits, osteonecrosis of the jaw (ONJ) may be the serious side effect associated with these agents.

In 2012, the World Health Organization (WHO) stated that there were 14.1 million new cancer cases and 8.2 million cancer deaths in the world.[4] Accordingly, the prescription rate of such medications increased. With the beginning of the present century, many cases of bisphosphonate-related osteonecrosis of the jaws (BRONJ) were reported by many researchers,[5-9] especially when BP was infused intravenously.[10] Denosumab, which is another antiresorptive agent, and the antiangiogenic agents like sunitinib were also found to cause jaw necrosis,[11,12] so the term "BRONJ" changed to medication-related osteonecrosis of the jaws (MRONJ) by the American Association of Oral and Maxillofacial Surgeons.[13]

MRONJ is a growing problem since the number of patients receiving bisphosphonates is increasing. In the UK, the incidence of MRONJ was 0.001%, as estimated in 2012, with number of dispensed prescriptions increasing by 2.5% over 7 years.[14] At the same time, the American Association of Oral and Maxillofacial Surgeons reported higher incidence of 0.004% in 2014.[13]

Although physicians prescribe these medications, they are not concerned in treating the side effects of the drugs, as patients resort to dental surgeons for treatment. That is why awareness of the side effects of antiresorptive and

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antiangiogenic agents and how to limit the incidence of MRONJ is crucial for medical specialists seen prescribing these drugs. This cross-sectional study aims to appraise MRONJ knowledge among Iraqi medical specialists.

Material and Methods

A cross-sectional based survey was performed among a sample of Iraqi medical specialists working in four Iraqi cites. The respondents were specialists in general surgery, urology, orthopedics, rheumatology, and oncology.

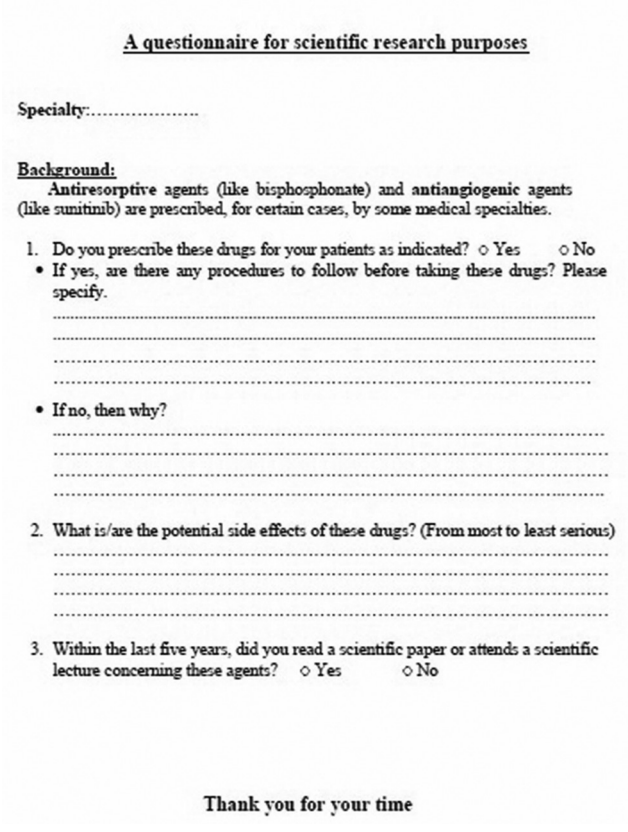
Over a period of 3 months, five trained dentists administered the questionnaires to specialists who were informed about the study protocol; the participation was voluntary and anonymous.

The questionnaire was designed to obtain an overview of the specialists' awareness and knowledge of MRONJ. After a brief description of antiresorptive and antiangiogenic agents, the questionnaire consisted of three questions (►**Fig. 1**):

1. Did you prescribe these drugs? ○Yes ○No

A. If yes, are there any procedures to follow before taking these drugs? Please specify.
B. If no, then why?

2. What is/are the potential side effects of these drugs?
3. Within the last 5 years, did you read a scientific paper or attends a scientific lecture about these agents?



A questionnaire for scientific research purposes

Specialty:.....

Background:
Antiresorptive agents (like bisphosphonate) and **antiangiogenic** agents (like sunitinib) are prescribed, for certain cases, by some medical specialties.

1. Do you prescribe these drugs for your patients as indicated? ○ Yes ○ No
   - If yes, are there any procedures to follow before taking these drugs? Please specify.
     .....
     .....
     .....
     .....
   - If no, then why?
     .....
     .....
     .....
     .....
2. What is/are the potential side effects of these drugs? (From most to least serious)
   .....
   .....
   .....
   .....
3. Within the last five years, did you read a scientific paper or attends a scientific lecture concerning these agents? ○ Yes ○ No

Thank you for your time

Fig. 1 Questionnaire used in study.

Only respondents who answered "yes" for the first question passed to the second question of the questionnaire; also, they answer a question that shed light on how they prepare their patients before starting drug intake. The second question addressed the detailed knowledge about the side effect of drugs. Respondents with the answer "no" were asked why they did not dispense these drugs. Question number three shows how specialists are interested in improving their information regarding these agents.

As the aim of our study focused on MRONJ knowledge, MRONJ-related answers were only considered. The questionnaires were completed and returned immediately. The data was analyzed using IBM SPSS Statistics for Windows (version 23, IBM Corp. Armonk, NY, USA). The significance of differences between the groups was assessed using analysis of variance (one-way ANOVA), and Duncan test considering probability values less than 0.05 as significant.

Results

One hundred and seventy-four specialists were asked to participate in the survey. Forty-two (24.1%) refused to participate compared with 132 (75.9%) who agreed. There were 40 urologists, 38 orthopedic surgeons, 36 general surgeons, 10 oncologists, and eight rheumatologists.

As far as the first question was concerned, 57 (43.2%) out of 132 respondents answered "yes." When asked as to how they prepare their patients before drug intake, only nine (15.8%) correct answers were recorded compared with 48 (84.2) wrong answers (►**Table 1**), with a significant difference recorded among groups in favor of the oncologists' group (►**Table 2**). As many as 75 (56.8%) specialists responded with the answer "no," and they provided multiple such as the following:

- These medications related to other specialties (38, 50.7%).
- Refer patients to oncologist (12, 16%).
- I do not know anything about these medications (7, 9.3%).
- I have not heard about these medications before (5, 6.7%).
- I have little information about these medications (2, 2.7%).
- I have never used these medications before (2, 2.7%).
- These medications may cause BRONJ (1, 1.3%).
- No answer given by eight respondents (10.7%).

Awareness about the side effects of antiresorptive and antiangiogenic agents was outlined by question 2, which again registered significantly more correct answers from the oncologists group compared with the other groups (►**Table 2**). However, all respondents recorded 15 (26.3%) correct answers and 42 (73.7%) wrong answers (►**Table 1**).

By answering the third question, 55 (41.7%) out of 132 specialists developed their knowledge on the topic in recent years (►**Table 1**). The results were significantly different among all groups, with the lowest rates recorded in the urologists' set (►**Table 2**).

Table 1 Respondents' answers of questions

Specialty	Q1		Q1. A		Q2		Q3	
	Yes *n* (%)	No *n* (%)	Correct *n* (%)	Wrong *n* (%)	Correct *n* (%)	Wrong *n* (%)	Yes *n* (%)	No *n* (%)
Urologists	3/40 (7.5%)	37/40 (92.5%)	0/3 (0%)	3/3 (100%)	0/3 (0%)	3/3 (100%)	9/40 (22.5%)	31/40 (77.5%)
Orthopedic surgeons	33/38 (86.8%)	5/38 (13.2%)	2/33 (6.1%)	31/33 (93.9%)	3/33 (9.1%)	30/33 (91.9%)	26/38 (68.4%)	12/38 (31.6%)
General surgeons	5/36 (13.9%)	31/3 (86.1%)	2/5 (40%)	3/5 (60%)	3/5 (60%)	2/5 (40%)	10/36 (27.8%)	26/36 (72.2%)
Oncologists	10/10 (100%)	0/10 (0%)	5/10 (50%)	5/10 (50%)	7/10 (70%)	3/10 (30%)	6/10 (60%)	4/10 (40%)
Rheumatologists	6/8 (75%)	2/8 (25%)	0/6 (0%)	6/6 (100)	2/6 (33.3%)	4/6 (66.7%)	4/8 (50%)	4/8 (50%)
Total	57/132 (43.2%)	75/132 (56.8%)	9/57 (15.8%)	48/57 (84.2%)	15/57 (26.3%)	42/57 (73.7%)	55/132 (41.7%)	77/132 (58.3%)

Table 2 Statistical analysis of respondents' correct/yes answers of questions

	Urologists group (1) *n* (%)	Ortho. S group (2) *n* (%)	GS group (3) *n* (%)	Oncologists group (4) *n* (%)	Rheuma. group (5) *n* (%)	ANOVA test	Duncan test		
							A	B	C
Q1.A	0/3 (0%)	2/33 (6.1%)	2/5 (40%)	5/10 (50%)	0/6 (0%)	.003*	1 5 2 3	3 4	
Q2	0/3 (0%)	3/33 (9.1%)	3/5 (60%)	7/10 (70%)	2/6 (33.3%)	.000*	1 2 5	5 3 4	
Q3	9/40 (22.5%)	26/38 (68.4%)	10/36 (27.8%)	6/10 (60%)	4/8 (50%)	.000*	1 3 5	3 5 4	5 4 2

Abbreviations: ANOVA, analysis of variance; GS, general surgeons; Ortho. S, orthopedic surgeons; Rheuma, rheumatologists.
*Significant ($p < 0.05$).

Discussion

MRONJ is one of many prominent complications in the oral and maxillofacial region,[13]which became a common problem since antiresorptive and antiangiogenic agents are used in many medical disciplines for the treatment of a wide variety of cases. Due to the worldwide increase in bisphosphonate therapy and dependence, the incidence of MRONJ continuously grew.[15] It was thought that awareness of the topic is the key to implementing preventative measures in this group of patients.[16] Therefore, efforts were made to increase perception and awareness of MRONJ among health practitioners. However, few studies were performed on medical doctors' awareness of MRONJ, and how well they refer their patients to dentists.[17] Researchers found that MRONJ is a predictable disease,[18,19] so it is widely accepted that prevention is the best measure of MRONJ treatment.[20]

The duration of drugs-dependent therapy and the route of their administration are important risk factors that physicians should take care of to prevent ONJ. Another risk factor is the trauma to the jaw (dental extraction, surgery to the jaws, dental infection and/or abscesses, their treatment by scaling and endodontic therapy, and ill-fitting prosthetic devices) which is considered as the initial step for ONJ. Therefore, prevention of MRONJ by maintaining excellent oral hygiene is the first step to avoid dental treatments such as extraction and surgery.[21]

This fact requires doctors to implement dental referrals to assess patients' oral health before beginning administration of related drugs to eliminate dental problems and the potential risk factors.[13,22,23] The long-lasting effect of these drugs on bone makes the routine dental assessment every 3 months mandatory, which is to be continued for the rest of the patient's life.[24]

This study is a complementary study to previous studies performed on dentists.[25,26] It surveyed Iraqi general surgeons, urologists, orthopedic surgeons, rheumatologists, and oncologists to assess their knowledge about MRONJ in the form of questionnaires.

Our findings showed that about half of the respondents did not prescribe these drugs, and most of them were urologists and general surgeons. They believed that these drugs were not related to their specialties, and some of them refer their patients to oncologists. However, they should be aware of ONJ, since they may prescribe or face patients suffering from this complication because of treatment by others.[27]

In contrast, all oncologists and most orthopedic surgeons and rheumatologists prescribe these medications. Low rate/absence of patient referrals for dental checkups before starting drug administration was seen in most groups, perhaps due to their ignorance of MRONJ, as is evident from the answers of the second question or because there is not adequate time for dental treatment, especially for advance cancer patients. Our results are consistent with another study in which different specialties were included.[17] On the other hand, oncologists showed the best rate of dental referral (50%), but this rate is still low. Other researchers, through a study performed on oncologists, reported a comparable moderate dental consultation.[28] In total, 84% of specialists in the current study did not consider dental referral in their treatment strategy. Other researchers[29] also reported a high rate (62%) of physicians who did not request dental advice.

It is imperative for medical specialists to be able to identify the risk of these agents in terms of providing appropriate advice and management for patients. Perception was significantly higher among oncologists. This may be due to their efforts to obtain more relevant information about the drugs that they prescribe. However, the need for knowledge improvement among those who recorded lower scores is paramount. The results of this study showed that almost all orthopedic surgeons, most rheumatologists, and 30% of oncologists were unfamiliar with MRONJ. Therefore, perhaps they are not responsible for treating these cases. This study showed that 58% of specialists did not update their knowledge about the topic since 5 years, which had an effect on patient's awareness regarding MRONJ side effects, and how to prevent the serious harmful effects of these agents.[30,31] Moreover, deficiency in physician's knowledge about MRONJ may result in failure in detecting the early stage of MRONJ, which may prevent the advanced destructive stages where the treatment becomes difficult to achieve.[24]

The number of screened specialists add a limitation to this study, which cannot certainly represent all medical specialists, nor can it exclude selection bias. Additional studies with a sufficient sample size along with studies from other medical societies may provide results that are more reliable.

Conclusions

The cooperation between the medical doctor and dentist is essential in the prevention, diagnosis, and treatment of MRONJ.[22] We think that extra focus on MRONJ is essential for medical students and specialists in their curriculum, and at the same time, strengthening MRONJ awareness and knowledge among specialists and patients using related medications.

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Conflict of Interest
None declared.

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