Monitoring adverse drug reactions associated with bisphosphonates therapy among Libyan patients treated in public hospitals: the case of osteonecrosis of the jaw

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Abstract: This study was carried out to identify ADE, associated with the use of both PO and IV Bps among Libyan patients. The results indicated that significant number of patients have suffered different ADRs when using this group of medicines, for long period of time including BRONJ. The study has introduced BRONJ as being one of the major bisphosphonate-associated risks that causes decline in patients' quality of life, and emphasized the importance of early detection of signs and symptoms associated with ONJ, thus reducing its incidence among Bps users. The results underlined the importance of investigating the prevalence of BRONJ among Libyan patients undergoing long-term Bps treatment, as has been emphasized by both TUH' chief maxillofacial surgeon who introduced the two cases of BRONJ in only one month and the oncology clinical pharmacist who together sensed the aggravating risk of the misuse of this group of drugs and stressed the need to develop special protocol to ensure safe treatment.The study also pointed out the importance of multidisciplinary health team, including a dentist and a pharmacist, to ensure safe and effective use of this group of medications. This study therefore opens the door to investigate the adverse consequences that face patients undergoing bisphosphonate treatment. It also introduces all precautionary measures that should be taken into consideration when prescribing and administering bisphosphonates.

Keywords: Bisphosphonates, Adverse drug reaction, Osteonecrosis of the Jaw, Adverse events

Introduction

Medicines are double-edged sword. Controlling the complications that may arise from using pharmacotherapy during fighting health problems is now becoming a great challenge. One of the major classes of drug therapy problems (DTPs) associated with the risks of using medicines is Adverse Drug Reactions (ADRs) (1). ADRs decrease patients' quality of life making these patients seek another treatment to relieve their new complaints, or just stopping their drugs which may further complicate their conditions. Pharmacovigilance, as the science and practice of medicines' use surveillance, is becoming instrumental for the detection of less common but more serious ADRs which hinder the treatment process.Since many ADRs are preventable, finding solutions to these problems will ensure that patients safely and effectively use their medicines and this will restore confidence in the healthcare system, leading to reduction in the total cost of health care and patient compliance to drug treatment (2). The widespread introduction of bisphosphonates (Bps) into clinical practice occurred after the US-FDA) approval of alendronate in 1995. This was largely driven by the use of this class of skeletal antiresorptive agents to treat postmenopausal osteoporosis (3).Nowadays, Bps is widely prescribed being a highly effective drug group in the treatment of osteoporosis associated with glucocorticoids use and malignancies metastatic to bone (4). Information from well-designed clinical trials clearly shows that Bps are highly effective at limiting the loss of bone mass, deterioration of bone microarchitecture, and increased fracture risk that occur with aging (5-9).Additional approved indications for Bps include other forms of osteoporosis (such as that which occurs in men, or is associated with glucocorticoid therapy), Paget disease of bone, multiple myeloma, hypercalcemia of malignancy and metastatic bone disease in breast, prostate, lung or kidney (10-16).Despite the importance of this group of medicines in treating all previously mentioned conditions, their use however is associated with many ADRs some of which are serious. It is well documented that the use of Bps may be accompanied by short and long-term adverse events (13, 17, 18).

Osteonecrosis of the jaw (ONJ)is one of the most serious risks and has got the greatest attention among other risks that bisphosphonates can cause. It is a bone disease that is defined as an area of dead or exposed maxilla and mandible jaw bone that does not heal within eight weeks after identification due to breakdown of localized areas of the jaw bone. This death is likely due to ischemia. It is usually associated with pain as a result of secondary bacterial

infection of the local surrounding soft tissue. The risk is greater for patients receiving high doses of IV Bps (mostly Zoledronic acid and Pamidronate), and it occurs mostly in patients who receive monthly dose of IV Bps for cancer, more than for patients who receive oral BPs for osteoporosis and Paget's disease (19-21).However, ONJ has been reported in osteoporotic patients who take oral Bps but these data are incomplete (19). Dentistry refer to this serious condition as Bisphosphonate-Related Osteonecrosis of Jaw (BRONJ) (20, 21).

There are many factors that potentiate the risk of developing ONJ. These include poor oral hygiene, invasive dental procedures after starting IV BPs, prolonged exposure to high IV BPs doses (19, 22),dental infection and trauma such as dental surgery which increase the need of bone repair thus increase the potential binding sites for Bps, resulting in local accumulation of the drug (21).In addition, there are co-factors that may be associated with ONJ pathogenesis. These includediabetes, smoking, dental extraction and concurrent medications (23). Over the past few years, the pathological problem of jaw bone necrosis associated with the use of Bps medications has caused great concerns to Libyan dentists treating this group of patients. Dentists have placed a great deal of responsibility on pharmacists, as medicines' experts, and physicians prescribing this class of medicines, to play an active role in monitoring their adverse events (ADEs) in order to reduce or prevent their risks. Therefore, this study is designed to shed some light on the occurrence of ADRs associated with the use of both oral (PO) and intravenous bisphosphonates (IV) among patients treated in Libyan public hospitals.The study focuses on the incidence of BRONJ among BPs-treated patients and the introduction of the guidelines concerning the proper use of this group of medicines for the purpose of improving their benefits and reducing risks thus improve patients' quality of life and enhance patient compliance.

Materials and Methods

The study was carried out prospectively for a period of 4 months (August - November of 2018) in two outpatient departments (OPD) prescribing this class of medicines to their patients, namely adult oncology and rheumatology OPDs at both Tripoli University Hospital (TUH) and Tripoli Central Hospital (TCH). Sabrata Oncology Center was also included in the study in later time. Patients were interviewed and several

questionnaires (Qs I, II and III), adapted from "the Libyan Ministry of Health Pharmacovigilance Card" which was modified by adding specific questions related to Bps use and ADRs, were formulated. These questionnaires were directed to both patients and physicians to suit the purpose of each step of the study. Patients' files were also accessed to collect and verify some information about medication use and disease status. The working team consented to patients' right for confidentiality and privacy of their information. QI was directed to 30 randomly selected patients who received I.V.zoledronic acid, on the oncology department in the period specified. The same questionnaire was also directed to six patients receiving oral bisphosphonates at the rheumatology OPD, in order to assess the seriousness of ADRs among both cancer and osteoporotic patients. Patients were personally questioned regarding their trust in their healthcare providers and personal patients' consents were obtained throughout the study. Q II was directed to oncologists in all three hospitals while Q III was directed to rheumatologists at the OPDs of both TUH and TCH.

Questionnaire I: Bisphosphonates ADRs Detection

Date_____ Name _____ Age _____

Weight (Kg) _____ Gender:M \ F Is the patient pregnant? Yes \ No

Generic name of the used medicine_____

Brand name (if any)_____

Route of administration: ____ PO or I.V Dose _____

Indication: (Osteoporosis/Type of cancer/ any other condition)

Specify_____

Date medication started: _____ Date stopped (if any)_____

Other diseases:

_____

__

Other Medications (including OTC)

_____

When do you take yourBps pill? Morning Evening

Do you take your medicine on an empty stomach? Yes No

Do you drink milk or juice with the pill? Yes No

Do you take your Ca supplements with your oral Bps?Yes No

What is your body posture when administrating oral Bps erect position supine position?

What do you do if you ever missed your dose?_____

Did your physician or pharmacist give you advice on how to take your Bps medicine?

_____

Have you experienced any of the following ADRs?

Adverse drug reactions	No	Yes	If Yes, comment (date reaction started /date stopped)
Esophageal erosions or			

esophagitis			
Any GIT ulcers			
Dry mouth			
Musculoskeletal pain (Bone, joint, muscle)			
Flu-like symptoms: (pyrexia, asthenia, fatigue or malaise)			
Taste disturbances			
Hyperesthesia			
Tremors			
ONJ and any infection before?			
Any fractures or osteonecrosis of other bones			
Eye inflammations			
Acute asthma exacerbations			
Increased sweating			
Weight increase			

Questionnaire II: Intravenous (IV)Bps therapy questionnaire directed to oncologists

1. What is the total number of oncologists in the hospital? Of those, how many prescribe BPs medicines to their patients?
2. In what cases are bisphosphonates prescribed and what dosages/dosage forms are used?
3. What cases are prescribed IV bisphosphonates medications?
4. What medical tests are requested to determine the period of treatment with IV Bps (starting to end date)

5. What should the patient avoid during treatment with IV Bps?
6. How long is the follow-up to the detection of patient's kidney function?

Every 2 weeks every month every 2 months (please specify otherwise)

7. What are the measures taken if the patient did not receive his/her dose on time?
8. Is patient alerted if any new bone pain, numbness or swelling in the jaw or any other side effects appeared?
9. Do you practice changing the 4 mg/month dosage regimen 4 mg/ 3 months? When this is done?
10. What precautions should the patient follow to avoid occurrence of ONJ?
11. What actions are taken in the event of ONJ occurrence?
12. What is the maximum period for which IV Bisphosphonate can be given?

Questionnaire III: Oral (PO) Bps therapy questionnairedirected to rheumatologists

1. What is the total number of rheumatologists in the hospital? How many of thoseprescribe oral bisphosphonates to their patients?
2. What cases are prescribedoral bisphosphonates? What are the doses/dosage regimen
3. What medical tests are requested to determine the period of treatment and when to end it?
4. What should the patient avoid during oral BPs treatment?
5. What directions should a patient follow while taking the medication?
6. How long is the follow-up to the detection of kidney function of patients?
7. Every 2 weeks every month every 2 months please specify otherwise
8. What are the measures taken if the patient forgot to take the dose on time? Weekly VS monthly dose(i.e.Patient exceeds the date of taking the medicine)
9. Do patients taking oral bisphosphonate have esophageal problems or stomachulcers?
10. Have any cases of ONJ appeared in osteoporotic patients treated with BPs? If yes, how many cases are documented?
11. Do you practice "medicines holiday" (not prescribing the medicine for a certain period of time, then re-introducing it back)?
12. What is the longest period of time to prescribe this medicine for osteoporotic patient?

Results

Findingsare summarized in tables 1 to 4. Of the randomly selected 30 patients who answered questionnaire I and who were administered 4 mg IV dose of zoledronic acid **(**Zometa®**)** monthly at TUH oncology OPD, 23 (77%) of them were female ranging in age between 31-53 y while 23 % (7 patients) were male. Only 30% of female patients are diabetic (Type II)in comparison with 57% of male.The medicine was indicated for the treatment of bone metastasis resulted fromprostate cancerin male patients, while in 22 of the 23 female patients, the drug was indicated for bone metastasis resulted from breast cancer, and one patient was suffering from multiple myeloma.All interviewed patientsstated that they trust their healthcare provider and adhere to their instructions when taking their medicine. Patients stated that when the injection is not available at the hospital, they madesure to buy it from private pharmacies. They added that they do not care to obtain the recommended brand, especially if they cannot afford its pricetherefore,they buy the cheaper one.

Table 1: Recorded ADRs Associated with IV Zoledronic acid

Adverse Drug Reaction	***No. of patients Suffered ADRs**	**Percentage %**
Musculoskeletal pain	18	60%
Dry mouth	12	40%
Flu-like symptoms	12	40%
Hyperesthesia	12	40%
Increased sweating	11	36.66%
Jaw pain	9	30%
Taste disturbances	6	20%
Tremors	3	10%
GIT ulcers	2	6.66%
Eye inflammations	2	6.66%
Acuteasthma exacerbations	2	6.66%
Weight increase	2	6.66%

*n = 30

Table 2: ADRs associated with oral Bps

Adverse Drug Reaction	No. of patients who Suffered ADRs	Percentage of occurrence
Dry Mouth	4	67%
Musculoskeletal Pain	3	50%
Tremors	3	50%
Hyperesthesia	2	33.3%
Increased Sweating	2	33.3%
Eye Inflammations	1	16.6%

When asked about physician's recommendation regarding their teeth, clearly not all patients were told to have dental check-up before starting BPs therapy, nor were advised against dental work during I.V. Bps treatment. This was confirmed by TUHdentistswho facedBRONJ's dilemma. In addition, very few patients were warned againstthe possible ADRs that they may suffer as a result of using I.V. BPs therapy in general.Of the 30 patientsinterviewed, two were introduced by the head oral and maxillofacial surgeon at TUH upon our request. These two patients are suffering from ONJ and have been using I.V.zoledronic acid for about 10 years.Q-I was also answered by six female patients taking oral Bps. Patients were ranging in age between 46-70 years, five of which are taking alendronate (Fosamax®) and only one patient is receiving risedronate. The medicinewasprescribed for the treatment of osteoporosis and as preventative measure. Four of the six patients said that they are taking their medicine in the morningand two did not care about the right time for its administration. All patients take the medicine on an empty stomach except one.

Table 3: Answers to questionnaire II, directed to oncologists

Tests performed to decide duration of therapy	10 oncologists requested KFT 12 oncologists added Ca serum test 1 oncologists added DEXA scan 3 bone MRT/C.T. scan 7 oncologists added Bone Isotopic Scan
Things to avoid during IV BPs therapy	12 oncologists suggested to avoid teeth surgical intervention/dental extraction and 6 oncologists had a reservation to answer
When to perform KFT	All 18 oncologists suggested the request of KFT q. 3-4 Weeks
Do oncologists ask their patient for follow-up evaluation if jaw pain or swelling occurs	15 answered with "Yes" 2 answered with "No" and 1 abstained

Change in dosage regimen	12 oncologists answered with "Yes" 3 answered with "No" and 3 had a reservation to answer
Precautions to avoid ONJ	11 oncologists suggested to avoid dental procedures and follow-up with a dentist 3 answered with "No precautions" and 4 abstained
If ONJ occurs	13 oncologists suggested to stop Bps and follow-up with a dentist 1 suggested that patients has to take the medicine every month 4 abstained to answer
Maximum duration of IV BPs	2 oncologists answered "Lifelong" 5 answered "No specific time if there were no complications" 7 answered "2 years and sometimes longer" 1 answered "6 months to 1 year" 3 had a reservation to answer

Table 4: Answers to questionnaire III directed to rheumatologists

Tests performed to decide duration of therapy	Physicians requested Kidney Function Test (KFT) and one added Ca serum and vitamin D levels.
Things to avoid during oral BPs therapy	One suggested avoiding laying down an hour after taking the medicine.One suggested "nothing to avoid",
When to perform KFT	Physicians suggested the request of KFT q. 6 months
Directions of use	1 physician suggested taking Ca supplements 1 physician suggested drinking plenty of water

What to do when dose is missed	Physicians suggested that patients should take it as soon as they remember
GIT problems	Physicians answered that they occur in some cases, but insisted that GIT problems won't occur if patients stick to directions of use
Drug holidays	Physicians suggested drug holidays in some cases

When patients were asked what to do if they forget their weekly dose, they answered that they take it once they remember. No one mentioned that she should follow specific regimen recommended by the physician or pharmacist. All of them take oral BPs with water while sitting.Calcium supplement was taken by all 6 patients, four of which are taking it at different timing from taking Bps, but two were taking thecalcium supplement together withthe medicine.Only five patients acknowledged that their physician briefly told them how to take the drug.Patients taking oral Bps were questioned about ADRs that they may have encountered during their treatment. Six ADRs have recorded as shown in table 2.Out of 36 oncologists at TUH, only five agreed to answer questionnaire II in addition to other 2 oncologists in TCH. Answers to Q IIwere also obtainedat later time, from 11 out of 29 oncologists who are prescribing Bps at Sabrata Oncology Center (SOC). That madea total of 18 oncologists who participated in this study. The questionnaire is made of 12 questions with short answers, and the physicians were allowed enough time to answer them. Table 3 summarizes all answers.With regards to rheumatologists'answers to questionnaire III**,** only two physicians accepted to answer the questionnaire, one in each hospital. Table 4 containsa brief summary to their answers.

Discussion

This study identified ADRs associated with the use of both PO and IV Bps among Libyan patients. The results indicated that significant number of patients have suffered

different adverse effects when using this group of medicines for long period of time. The study introduced BRONJ as being one of the major bisphosphonate-associated risks that causes decline in patients' quality of life, and emphasized the importance of early detection of signs and symptoms associated with ONJ thus reducing its incidence among Bps users. The results underlined the importance of investigating the prevalence of BRONJ among Libyan patients undergoing long-term Bps treatment which was emphasized by both the chief maxillofacial surgeon in TUH, who introduced 2 cases of BRONJ in only one month, and the oncology clinical pharmacist who sensed the aggravating risk of the misuse of this group of drugs and stressed the need to develop special protocol to ensure safe and effective treatment.The study also pointed out the importance of multidisciplinary health team including a dentist and a pharmacist, to ensure safe and effective use of this group of medications. Thus, the following recommendations should be considered when prescribing/taking Bps:evaluation and correction of hypocalcemia and/or vitamin D deficiency prior to starting Bps treatment(25, 26).Treatment should be delayed in patients who are undergoing any invasive dental procedure including; dental implant or extraction for a few months until healing of the jaw is complete.Dentists should advise patients who are taking BPs and at a risk of developing ONJ to maintain good oral hygiene and to have regular dental check-up. Dental examination is necessary for those who have poor dental health before starting PO treatment (27).Patients should be counseled and continuously encouraged to take their oral Bps by showing them the importance of adherence to their medication, since noncompliance occurs after the first year of treatment.Patientsshould be informed about the proper method of administration, and what to avoid when taking the medicine.In addition, Bps are contraindicated for patients with active GI disease and should be discontinued in patients who develop any symptoms of esophageal irritation such as difficulty or pain upon swallowing, pain in chest, or new or worsening heartburn (27). Because of concerns about serious risks associated with long-term antiresorptive therapy, osteoporotic patientsshould not be prescribed Bps for more than three years (for I.V. zoledronic acid) and five years (for POalendronate and risedronate). Reassessment of fracture risk at the end of the infinite treatment period is important

because some patients still at high risk of fracture therefore, they need to continue treatment. Osteoporotic patients may benefit from "Drug Holiday" to reduce the risk of atypical fractures of the thigh bone. Thisis done on an individual basis (28, 29).When a weekly dose is missed, it should be taken the second day, but if it was missed for more than one day,patient has to skip the dose to the next week (30, 31).When a monthly doseis missed, the patient can take it within seven days before the next administration (31).

To avoid the occurrence of ONJ, the following precaution should be taken into consideration prior to starting treatment with Bps:Dental check-up should be requested. TheAmerican Association of Oral and Maxillofacial Surgeons (AAOMS) Taskforce on BRONJ recommended that every patient should undergo dental evaluations and receive the necessary treatment before initiating IV BPs therapy (21).Calculation of Cr.Cl on basis of actual body weight (using Cockroft-Gault formula) before introducing I.Vzoledronic is necessary to ensure that it is not less than 35ml/min whichconfirm that there's no significant renal impairment.IV administration of zoledronic acid 4mg should be infused over >15 minutes (32).In order to minimize ONJ occurrence and renal toxicities in patients with bone metastasis from breast cancer, the I.V. zoledronic acid dosing regimen can be changed from 4mg every 3-4 weeks (1 month) to 4mg every 12 weeks (every three months). Studies have concluded that the "every 12 weeks regimen" of zoledronic acid was non-inferior to the "every four weeks regimen" in terms of efficacy and safety (33, 24). This change improves patient's quality of life. The consequences would be that patients have more time to spend with family and lead a normal life. It also means less money to spend and less visits to hospitals.Oncologists should pay more attention to patients who underwent IV treatment for more than 4 years, and those who have other co-factors that contribute to ADRs such as diabetes as those patients are more prone to ONJ.Re-evaluation of each patient's condition may be necessary to tailor medication therapy. Patients may also benefit from drug holidays.

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