

MISE AU POINT/IN-DEPTH REVIEW

BENEFITS AND POTENTIAL RISKS OF BISPHOSPHONATE THERAPY

A Narrative Review

<http://www.lebanesemedicaljournal.org/articles/64-4/review3.pdf>

Lana EL OSTA^{1*}, Nada EL OSTA², Hazem EL OSTA³

El Osta L, El Osta N, El Osta H. Benefits and potential risks of bisphosphonate therapy: A narrative review. *J Med Liban* 2016; 64 (4): 228-237.

ABSTRACT • Bisphosphonates have been proven to be effective and safe to millions of osteoporotic and cancer patients but were associated with multiple complications. The most prevalent and well established are upper gastrointestinal discomfort for oral bisphosphonates and acute phase reactions for intravenous forms. Although rare, hypocalcaemia and renal injury could be potentially serious. Severe musculoskeletal pain and ocular events may be ignored by physicians, which delay their diagnosis and management. Recently there are growing concerns over two long-term and emerging adverse effects, which are still of unclear pathophysiology and unproven causality. Osteonecrosis of the jaw is more common in cancer sufferers who receive high doses of intravenous bisphosphonates. Atypical femoral fractures are very rare compared with osteoporotic fractures that bisphosphonates prevent. Based on current data, the association of bisphosphonates with esophageal cancer, hepatotoxicity and atrial fibrillation remains doubtful. Overall, the adverse effect profile of these drugs is still unclear. Physicians must be vigilant to bisphosphonate-reported side effects and recognize the level of evidence supporting them, to better communicate the balance between benefits and potential risks to patients.

Keywords : bisphosphonates therapy; osteoporosis; oncologic bone disorders; side effects

INTRODUCTION

Bisphosphonates are the best known of the antiresorptive therapies, and consequently represent useful drugs for the treatment of metabolic and oncologic bone disorders [1-3]. Their therapeutic use has been increasing steadily in the last decade as well as their long-term use in clinical practice. This follows the introduction of easier dosing regimens, the availability of lower-priced generics, the worries about the safety of hormone-replacement therapy and the ageing of the population. In the United States alone, an estimated 80 million people take a bisphosphonate for cancer and osteoporosis, and

El Osta L, El Osta N, El Osta H. Les avantages et risques potentiels d'un traitement par bisphosphonates : Revue narrative. *J Med Liban* 2016; 64 (4): 228-237.

RÉSUMÉ • Les bisphosphonates ont prouvé leur efficacité chez un grand nombre de patients ostéoporotiques et cancéreux, mais ont toutefois été associés à de multiples effets secondaires. Les troubles gastriques liés à la forme orale, et le syndrome pseudo-grippal à la forme intraveineuse sont les complications les plus répandues et les mieux établies. Bien que rares, l'hypocalcémie et la néphrotoxicité pourraient être potentiellement graves. Les douleurs musculo-squelettiques sévères et les complications oculaires secondaires aux bisphosphonates pourraient être inexplorées par les médecins, retardant ainsi leur diagnostic et prise en charge. Récemment, deux effets indésirables émergent dans la littérature médicale : l'ostéonécrose de la mâchoire est surtout rencontrée chez les patients cancéreux recevant de fortes doses de bisphosphonates par voie intraveineuse ; les fractures fémorales atypiques en constituent un effet secondaire paradoxal. L'association des bisphosphonates avec le cancer de l'œsophage, l'hépatotoxicité et la fibrillation auriculaire reste douteuse. Globalement, le profil des effets indésirables des bisphosphonates demeure imprécis. Les médecins doivent être vigilants vis-à-vis des complications rapportées dans la littérature et doivent reconnaître le niveau de preuve à l'appui, afin de mieux communiquer les avantages et risques potentiels à leurs patients.

around 30 million bisphosphonate prescriptions are dispensed annually [4-5].

Bisphosphonates have a relatively good safety profile and are generally well tolerated. However, these benefits are associated with reports of multiple undesirable events, some of which may be serious and not previously recognized (Table I). Given the large and growing number of patients receiving bisphosphonates, physicians must be vigilant to bisphosphonate-reported side effects and recognize the level of evidence supporting them to better communicate the balance between benefits and potential risks to patients, in the hope of further increasing the safety of a therapy that has been proven to be effective to numerous patients.

In this manuscript, a brief overview of the pharmacology, mechanisms of action, and therapeutic uses precedes a more detailed discussion on the bisphosphonates-reported side effects, their characteristics, occurrence, risk factors, evidence on how to treat or prevent these events, and particularly the level of evidence supporting them.

¹Department of Public Health, School of Medicine, Saint-Joseph University (USJ), Beirut, Lebanon,

²Department of Prosthetic Dentistry, School of Dentistry, USJ.

³Department of Hematology-Oncology, Louisiana State University Health Sciences Center, Shreveport, LA, USA.

*Correspondence: *Lana El Osta, MD, MSc.*

e-mail: lanasta@hotmail.com; lane.osta@usj.edu.lb

The long-term use of bisphosphonate in osteoporosis and the need for drug holidays are also reviewed.

DATA SOURCES AND ARTICLES SEARCH

Medline database was searched through PubMed up to September 2014 for relevant articles using the following *keywords*: bisphosphonate therapy • oral bisphosphonates • intravenous bisphosphonates, in combination with indications including • osteoporosis • bone malignancies • bone metastasis • multiple myeloma, as well as side effects including • adverse events • complications • safety • acute-phase reactions • gastrointestinal intolerance • atypical fractures • osteonecrosis • nephrotoxicity • ocular inflammation • musculoskeletal pain • hypocalcaemia • atrial fibrillation • esophageal cancer.

References of the retrieved articles were also checked for additional references. We only considered English-language and French-language articles.

PHARMACOLOGY AND MECHANISMS OF ACTION

Bisphosphonates are powerful inhibitors of osteoclastic activity, with low intestinal absorption and high affinity for hydroxyapatite crystals. Bisphosphonates that are not taken up by the bones are excreted through the kidneys without metabolic alteration. Their biological half-life exceeds 10 years, and prolonged use can result in a substantial accumulation in the skeleton [6]. They are available as oral and intravenous formulations.

Bisphosphonates are not all the same. The non-amino bisphosphonates (etidronate, clodronate, tiludronate) promote the intracellular conversion of adenosine triphos-

phate to cytotoxic analogues, which lead to the immediate death of osteoclasts. The amino-bisphosphonates (pamidronate, alendronate, risedronate, ibandronate, zoledronate) cause osteoclasts apoptosis by inhibiting the farnesyl pyrophosphate synthase, a key enzyme of the mevalonate pathway of cholesterol synthesis, causing a breakdown of the osteoclast cytoskeleton and proliferation. The addition of nitrogen increases the potency of the drug [7-9].

Bisphosphonates have also anti-inflammatory, anti-angiogenic and anti-tumor effects, including induction of tumor cell apoptosis, inhibition of tumor cell adhesion to the extracellular matrix, and inhibition of tumor invasion [10].

THERAPEUTIC USES AND BENEFITS

Osteoporosis

Millions of patients are taking medications for postmenopausal osteoporosis, which represents actually a major health care issue. The most frequently prescribed drugs remain the bisphosphonates [4, 11-12].

Bisphosphonates currently approved by the FDA for the treatment and/or prevention of postmenopausal osteoporosis are: oral nitrogen-containing bisphosphonates (alendronate, risedronate and ibandronate) and low dose intravenous ibandronate and zoledronate. All except ibandronate are approved in both men and women [13]. Several studies have documented their efficacy in bone loss prevention and fractures reduction: In the United States, hip fracture rates have declined by 30% coincident with bisphosphonate use [14]. These drugs are also highly effective and commonly used in the treatment of

TABLE I REPORTED SIDE EFFECTS RELATED TO BISPHOSPHONATES USAGE AND THEIR MAGNITUDE

ADVERSE EVENTS	MAGNITUDE OF EFFECTS
Common	
Upper gastrointestinal intolerance	72-956 events per 1,000 persons for mild upper gastrointestinal side effects [11] 13.6 per 1,000 person-years for upper gastrointestinal bleeding [27]
Acute phase reactions	42.4% with zoledronate versus 11.7% for placebo [29]
Rare	
Severe musculoskeletal pain	2% to 5% of osteoporotic patients taking an oral bisphosphonate once a week [32]
Ocular inflammation	44-45 per 1,000 patient-years [36]
Hypocalcaemia	5-118 events per 1,000 persons with zoledronate (85% of patients did not require supplemental calcium) [11]
Renal toxicity	Oncology: 9.3% with zoledronate versus 8.1% for pamidronate [43] Osteoporosis: 1.8% with zoledronate versus 0.8% for placebo [44]
Emerging	
Atypical femoral fractures	2.3 per 10,000 patient-years [12, 50]
Osteonecrosis of the jaw	Oncology: 1-12% at 36 months of exposure [55] Osteoporosis: 1 case per 100,000 person-years [55]
Uncertain	
Esophageal cancer	< 1/1,00,000 patient-years of exposure [59]
Hepatotoxicity	Few cases have been reported in the literature [60]
Atrial fibrillation	< 1/1,000,000 patient-years with risedronate [59]

osteoporosis induced by hormonal therapy in cancer (androgen deprivation for prostate cancer and aromatase inhibitors for breast cancer) [15-16].

Fracture risk reduction with long-term bisphosphonate treatment for osteoporosis

Bisphosphonates have been studied in clinical trials of at least three years in duration with fractures assessed as the primary end point. The registration trials of alendronate, risedronate and zoledronate were subsequently extended for up to 10 years to investigate the long-term efficacy and safety of these drugs.

The Fracture Intervention Trial Long-term EXtension (FLEX) [17] compared the effect of 10 years of continuous alendronate treatment with cessation of therapy after five years of initial treatment, among postmenopausal women with osteoporosis. Those who continued alendronate for 10 years had fewer clinical vertebral fractures (2.4% vs. 5.3%; relative risk, 0.45; 95% Confidence Interval (CI), 0.24-0.85). However, there was no difference in rate of morphometric (also called asymptomatic or radiographic) fractures.

The first extension study of the 3-year Vertebral Efficacy with Risedronate Therapy – MultiNational (VERT-MN) trial [18] found a significantly lower risk of morphometric vertebral fracture among postmenopausal women who received risedronate therapy for two additional years (relative risk reduction, 59%; 95% CI, 19%-79%).

In the Health Outcomes and Reduced Incidence with Zoledronic acid ONce yearly – Pivotal Fracture Trial (HORIZON-PFT) extension [19], postmenopausal women with osteoporosis who received zoledronate for three years were randomized to three additional years of zoledronate or placebo. Morphometric vertebral fracture rates were lower among those who continued versus those who stopped zoledronic acid after three years (3.0% vs. 6.2%; odds ratio, 0.51; 95% CI, 0.26-0.95).

Moreover, there is strong evidence supporting vertebral fractures reduction efficacy in osteoporotic women for alendronate, ibandronate, risedronate and zoledronic acid. However, there is less evidence supporting nonvertebral fracture reduction efficacy for ibandronate than for the other bisphosphonates [11].

Malignancy

Bisphosphonates are beneficial for malignancy-related bone disorders including multiple myeloma, bone metastases and hypercalcaemia of malignancy. They involve higher doses and frequency of drug administration, and are mainly administered intravenously. The two intravenous bisphosphonates approved by the FDA are zoledronate and pamidronate. Ibandronate is approved in Europe for cancer indications [20]. Clodronate may also be used in patients with oncologic bone disorders [21-22].

The use of bisphosphonates in oncology is palliative, because they have not been reliably shown to improve survival or prevent bone metastases. Cancer patients can

benefit greatly from their therapeutic effect by controlling bone pain and reducing the incidence of other skeletal complications as pathologic fractures, spinal cord compression, hypercalcaemia of malignancy, and the need for subsequent radiation therapy or surgery to bone [23-24]. Moreover there is an emerging evidence for direct and indirect anti-tumor activity of bisphosphonates, and potential synergy with anti-cancer drugs [10, 25].

ADVERSE EVENTS OF BISPHOSPHONATE THERAPY

The adverse effects profile varies greatly between bisphosphonates. It depends on a number of factors, such as the pharmacologic properties of the drug, its indication, its dose, as well as its route, frequency and length of administration.

Gastrointestinal adverse events

Upper gastrointestinal (GI) toxicities (nausea, vomiting, epigastric pain, dyspepsia, esophagitis) are seen with oral amino-bisphosphonates and are generally mild. They are due to mucosal irritation of the upper GI tract. Randomized controlled trials (RCTs) suggest little or no increase in GI side effects if patients adhere to the dosing instructions. They propose that many of these complications may reflect a high background incidence of upper GI complaints and an increased sensitivity to detection rather than a causal relationship to therapy [26]. A recent systematic review [11] showed an increased risk for mild upper GI side effects with use of alendronate (OR, 1.07; 95% CI, 1.01-1.14).

Esophageal erosions and ulcerations, and upper GI bleeding are extremely rare life-threatening complications. A population-based nested cohort study performed in Canada exposed an incidence rate of 13.6 per 1,000 person-years for upper GI bleeding within 120 days of incident bisphosphonate prescription. This incidence was much higher in patients > 80 years of age [27].

GI-related adverse events are cited as a major reason for discontinuation of bisphosphonates. However, they are rarely the cause of withdrawal in RCTs [1, 11, 17-18].

Multiple conditions including upper GI bleeding, ulcer disease, esophageal or gastric varices, and Barrett's esophagus should be considered as relative contraindications to oral bisphosphonates. Large hiatal hernia with moderate to severe gastroesophageal reflux, and esophageal emptying disorders are more complete contraindications to oral forms.

Oral non-amino bisphosphonates produce fewer upper GI problems but more diarrhea and abdominal distention compared to amino-bisphosphonates [21].

Overall, oral bisphosphonates have good GI tolerability. If the patient presents a contraindication to the oral form and/or if GI disorders persist despite the adherence to the dosing directives, administration should be switched to the intravenous route.

Acute phase reactions

Acute phase response (APR) is the most prevalent complication of intravenous amino-bisphosphonates. It is a nonspecific physiologic reaction, described as flu-like and related to proinflammatory cytokines release: tumor necrosis factor α and interleukin 6, by T cells in response to amino-bisphosphonates [28].

Approximately 40% of patients receiving intravenous bisphosphonate experience an APR which mainly occurs after the first infusion, and typically lasts 2 to 3 days. Reid *et al.* [29] analyzed the adverse events occurring within three days of zoledronic acid infusion from the HORIZON-PFT. The treatment was associated with more than 30 adverse events that were regarded collectively as constituting an APR. They were grouped into five symptom clusters: fever, musculoskeletal, gastrointestinal, eye, and general. A composite of these symptoms called APR occurred in 42.4% of the zoledronic acid group and 11.7% of placebo. However, fever, musculoskeletal, gastrointestinal, eye, and general symptoms occurred in 20.3%, 19.9%, 7.8%, 0.6%, and 21.9% of zoledronic acid-treated subjects, respectively.

APR may rarely occur after the initial exposure to once-weekly or once-monthly oral amino-bisphosphonates [30], and has not been reported with the non-amino bisphosphonates.

Symptoms are usually self-limiting and symptomatic treatment with analgesics and antipyretics is often helpful [28]. However, they can be very distressing, thus causing treatment withdrawal.

Severe musculoskeletal pain

After receiving reports of severe musculoskeletal pain in patients treated by bisphosphonates, the FDA issued in January 2008 a warning emphasizing the possibility of severe and sometimes debilitating bone, joint and/or muscle pain that may occur within days, months or years after bisphosphonate initiation [31]. In contrast to the APR, this complication is rare. It affects between 2% and 5% of patients, especially those taking an oral bisphosphonate once a week [32]. Its exact incidence, risk factors and pathological credibility are still undetermined [33-34].

In case of severe musculoskeletal pain, healthcare professionals should consider temporary or permanent discontinuation of the treatment rather than escalation of analgesic therapy [34].

Ocular events

Although rare, ocular inflammatory reactions may occur with all types of bisphosphonates. The most common presentation is conjunctivitis, which usually is self-limiting. Uveitis, scleritis, keratitis and global orbital inflammation, quite rare, are associated with major morbidity and require drug discontinuation [35]. More than one ocular side effect can happen simultaneously. Presentation could be unilateral or bilateral. Symptoms often occur after an APR, and thus, may represent a localized mani-

festation of a systemic adverse reaction to the drug. They can also happen weeks, months, or even years after bisphosphonate initiation, and tended to appear earlier with intravenous formulations. The exact mechanism and incidence of this complication are not yet recognized. However, a large population-based cohort study performed by Pazianas *et al.* [36] showed that the eye steroid treatment rates in the first year of osteoporosis treatment were 44 (95% CI, 42-46) per 1,000 patient-years for alendronate and 45 (95% CI, 35-57) per 1,000 patient-years for risedronate. The incidence of hospital-treated uveitis was low, occurring in 0.7 (95% CI, 0.5-1.0) cases per 1,000 patient-years for alendronate or risedronate. Patients with a rheumatic or pulmonary disease were also at increased risk.

Early reporting of any signs of eye inflammation is advised to prevent further complications. In serious ocular conditions, urgent ophthalmologic referral is required. Physicians must use bisphosphonates with caution in patients suffering from rheumatic or pulmonary diseases [35-36].

SERIOUS ADVERSE EVENTS OF BISPHOSPHONATE THERAPY

Hypocalcaemia

Bisphosphonates can cause electrolyte imbalances, hypocalcaemia being by far the best recognized abnormality. Because of the low intestinal absorption of oral bisphosphonates, hypocalcaemia occurs most often after intravenous infusion: zoledronic acid was shown to be associated with an increased risk of hypocalcaemia (OR, 7.22; 95% CI, 1.81-42.70), however, 85% of patients did not require supplemental calcium [11]. While mild biochemical hypocalcaemia is common, several cases of symptomatic hypocalcaemia following intravenous and oral treatment were reported. It may lead to serious concerns among susceptible patients: seizure was described among patients with brain metastases and mild hypocalcaemia. Its onset varies from a few days to several months after treatment initiation [37].

Hypocalcaemia occurs mainly in patients with pre-existing hypoparathyroidism, impaired renal function, vitamin D deficiency, limited calcium intake, and hypomagnesaemia. These patient-related risk factors impair the normal compensatory mechanism of parathyroid hormone in response to the serum calcium decline after bisphosphonate therapy [38]. Disease-related risk factors such as massive bone metastases may predispose patients to hypocalcaemia due to intense calcium uptake into bone [39]. Bisphosphonate-related factors including intravenous route, potency, high-dose and short treatment interval also increase the risk of hypocalcaemia.

Before initiating bisphosphonate therapy, precipitating factors should be treated; calcium intake and vitamin D status optimized [20, 37]; recommended dosage and treatment interval respected.

Renal toxicity

With the use of intravenous non-amino bisphosphonates for the treatment of malignant hypercalcaemia, the first cases of renal failure emerged in the literature [40]. Subsequently, several cases were reported with pamidronate and zoledronate used to treat malignancy-related bone diseases. Retrospective studies revealed that the risk of nephrotoxicity might be higher with zoledronic acid than with pamidronate. In contrast, results from clinical trials indicated that intravenous ibandronate has a safety renal profile, even in patients with abnormal baseline kidney function and is not affected by the use of shorter infusion times or higher doses. Patterns of nephrotoxicity include toxic acute tubular necrosis with zoledronate, and focal segmental glomerulosclerosis with pamidronate [41-42].

The renal deterioration in cancer patients is probably precipitated by various risk factors including advanced age, progressive cancer, multiple myeloma, chemotherapy, concomitant nephrotoxic medications, previous treatments with bisphosphonates, severe dehydration, hypercalcaemia, hypertension, diabetes mellitus, or baseline renal impairment. Higher doses of bisphosphonates, shorter infusion durations and dose intervals lower than recommended are also important determinants of nephrotoxicity. The total dose administered during a long-term treatment could play a role because of its possible cumulative effect [41]. Intrarenal accumulation of bisphosphonates may contribute to the renal injury, although, the exact mechanism remains undetermined.

In a phase III trial comparing zoledronate to pamidronate that enrolled 1648 cancer patients, two protocol adjustments were required to reduce the incidence of renal insufficiency with zoledronate to a rate similar to that seen with pamidronate. Initially, patients were treated with intravenous zoledronate 8 mg infused over 5 min. The first protocol modification increased the infusion time from 5 to 15 min, whereas the second reduced the dose from 8 to 4 mg. Following the two protocol adjustments, the incidence of nephrotoxicity, defined as an increase in serum creatinine of at least 0.5 mg/dl, was 9.3% with zoledronate as compared to 8.1% for pamidronate [43].

Based on the available data, severe nephrotoxicity can be largely avoided by rigorous adherence to the following recommendations: monitor the renal function (serum creatinine) prior to each infusion, increase infusion length to 30 minutes, maintain adequate hydration, and avoid hypotension and concurrent nephrotoxic agents. If the patient has a preexisting chronic kidney disease, the doses should be reduced or a switch to more renally safe bisphosphonate such as ibandronate could be discussed. If the renal function deteriorates, treatment withdrawal should be considered. Intravenous bisphosphonates are generally not recommended in patients with severe renal impairment (creatinine clearance less than 30 mL/min) [37,44].

In postmenopausal osteoporosis, zoledronate and

pamidronate are associated with significantly less nephrotoxicity, which absolutely relates to the lower doses and longer dosing intervals. However, they should be carefully used in patients with impaired renal function. Based on the postmarketing cases of renal impairment and acute renal failure associated with zoledronic acid 5 mg received by the FDA, renal impairment section of the current label reports a transient increase in serum creatinine of at least 0.5 mg/dl occurring within 10 days of dosing in 1.8% of zoledronate-treated patients compared to 0.8% of placebo-treated patients [44].

To date, there is no evidence that therapeutic doses of oral bisphosphonates have been associated with significant nephrotoxicity. As bisphosphonates are eliminated through the kidneys, and in the absence of long-term prospective data in patients with osteoporosis and severe renal insufficiency (creatinine clearance < 30 mL/min), all bisphosphonate therapies have warnings or contraindications for use in patients with severe renal impairment [12,44].

Atypical femoral fractures

Initially, bisphosphonate therapy was not considered a predisposing factor of atypical femoral fractures (AFFs), which were supposed to be an uncommon subtype of osteoporotic fracture or a manifestation of a rare metabolic bone disease, the adult hypophosphatemia, with coincident bisphosphonate use. In 2005, Odvina *et al.* suggested that prolonged bisphosphonate exposure might lead to AFFs [45]. These fractures typically happen spontaneously or after low energy trauma, are occasionally preceded by prodromal tight pain or vague discomfort, and may have delayed or absent healing [46].

The association between bisphosphonates and AFFs was not identified in clinical trials. However, newest data from retrospective studies showed that these fractures are unusual adverse drug reactions associated with bisphosphonates, longer duration of treatment further increases the risk, and bisphosphonate withdrawal after long-term use lowers the risk [14]. Girgis and colleagues identified additional risk factors: history of low energy fractures, glucocorticoid therapy of six months or more, active rheumatoid arthritis, and low vitamin D levels [47]. Multiple hypothetical mechanisms were reported: long-term treatment could oversuppress the bone turnover, leading to alterations in bone mineral and organic properties, which probably increase skeletal fragility [48].

Based on all epidemiological studies published to date, the incidence rate of AFFs seen with bisphosphonates increased during the last decade. However, the absolute incidence rate is very low. Secondary analysis of data from FIT, FLEX and HORIZON that included more than 51,000 patient-years of follow-up for up to 10 years revealed that occurrence of AFF was similar among placebo- and bisphosphonate-treated women, with estimated incidence of AFF with bisphosphonate of 2.3 per 10,000 patient-years [49]. The FDA affirmed that

these fractures are uncommon, accounting for less than one percent of the hip and femur fractures that occur in the population overall [50]. The benefit to risk ratio of bisphosphonate use remains positive despite an increased risk for these fractures.

Currently there is no consensus about management of AFFs. The FDA recommends that healthcare professionals be aware of the possibility of AFFs in patients taking bisphosphonates. The prodromal thigh or groin pain should lead to radiographic examination of the femur to rule out a femoral fracture. In the event of a documented fracture, bisphosphonate treatment should be discontinued and a radiographic examination of the contralateral femur considered [14]. Experts recommend daily calcium, vitamin D supplementation, and teriparatide therapy, which enhance fracture healing. In resistant cases, surgical options should be considered [46,48]. More work is required to determine the best approach to prevent, early identify and manage these fractures.

Osteonecrosis of the jaw

Bisphosphonate-induced osteonecrosis of the jaw has emerged over the last 10 years as an adverse effect of amino-bisphosphonates. It is a rare but potentially destructive complication. It adversely affects the quality of life, producing significant morbidity in affected patients, since chewing, speaking, and swallowing can be considerably and lastingly compromised [51]. It is defined as an area of exposed bone in the maxillofacial region that has not healed within eight weeks after identification in a patient who is receiving or has been exposed to a bisphosphonate without local evidence of malignancy and no prior radiotherapy to the affected region. The posterior mandible is the main affected site due to the high rate of bone remodeling [52]. A recent review of published controlled clinical trials between 2003 and 2010 shows that the incidence of bisphosphonate-induced osteonecrosis of the jaw is strongly dependent on the medication forms. It is estimated to be 0.12% with the oral route overall, and 7% with the intravenous forms overall. However, the exact incidence remains unknown because of the weakness of study designs, most of them being retrospective and using mixed samples during short follow-up [53].

Based on the biological activity of bisphosphonates, this complication could be linked to the drug-induced remodeling suppression, hypocellularity and hypovascularization of the bone, microbial infections, and cytotoxicity of the keratinocytes of the oral mucosa [54]. Numerous risk factors have been reported; the two most important are the intravenous form and dentoalveolar procedures. More than 95% of cases reported in the literature have occurred in cancer patients receiving long-term, high-dose, intravenous bisphosphonate, in whom the estimated incidence is 1-12% at 36 months of exposure. Osteonecrosis of the jaw in patients receiving low-dose bisphosphonate for osteoporosis is very rare, with estimated incidence rate of less than 1 case per 100,000

person-years. Moreover, it is less aggressive, more predictable, and more responsive to treatment [55]. Thus, the benefits of using bisphosphonate drugs in preventing fractures associated with osteoporosis by far outweigh the risk of osteonecrosis of the jaw.

The diagnosis is primarily based on the patient's history and clinical examination. There is little need for diagnostic imaging in patients with overt clinical picture. The clinical presentation may include pain, soft tissue swelling and ulceration, suppuration, paresthesia, exposed bone and teeth loosening. Periodontal disease, gingivitis, mucositis, osteomyelitis, sinusitis, periapical pathology, osteoradionecrosis, neuralgia-inducing cavitation osteonecrosis and bone tumors or metastases should be considered as differential diagnosis [52].

Because no long-term and controlled clinical trials on the management of this complication have been published, the current management has been suggested by expert medical societies. Treatment is directed toward pain control, infection management, bisphosphonates interruption and careful local debridement of necrotic bone, which are preferable to aggressive surgical procedures. Prevention is still the most effective way to limit the development of this complication, since healing is difficult to achieve. It mainly comprises removing all foci of dental infection before starting a bisphosphonate [52,56].

Bisphosphonate-induced osteonecrosis of the jaw has not been observed with non nitrogen-containing bisphosphonates. Moreover, patients with an established osteonecrosis of the jaw may be switched to oral clodronate [52].

Overall, physicians need results from basic research and controlled clinical studies, to better understand and manage this disease.

Bisphosphonates-related complications and particularly their biological plausibility and causality link are reviewed in Table II.

Improbable complications

The link between oral amino-bisphosphonates and esophageal cancer has recently received growing concern, and related studies have generated conflicting results. Accordingly, the FDA stated in July 2011: "*no conclusion can be reached as to whether long-term use of bisphosphonates is associated with esophageal cancer*" [50]. Recently, two large studies were also consistent with the FDA statement [57-58]. An analysis of over 15,000 patients identified in RCTs or postapproval surveys found rates of esophageal cancer similar to the background rates in the population, with an incidence < 1/1,000,000 patient-years of exposure [59]. Nevertheless, the FDA advocates physicians to educate their patients to follow the directions for taking oral bisphosphonates, as esophagitis and other potential precursors of cancer have been related, mainly in patients using the drugs incorrectly [50].

To date, few cases of hepatotoxicity induced by amino-bisphosphonates have been reported.

TABLE II BISPHOSPHONATES-ASSOCIATED SIDE EFFECTS AND CHARACTERISTICS

Side effects	Biological plausibility	BPs* incriminated	Causality link	Occurrence and risk factors
Upper GI** intolerance	Mucosal irritation of the upper GI tract	Oral amino-BPs	Established	GI tract diseases such as: esophageal emptying disorders, Barrett's esophagus <i>Non adherence to the dosing instructions</i> High background incidence of upper gastrointestinal tract complaints
Acute phase reaction	Proinflammatory cytokines released by peripheral blood $\gamma\delta$ T cells	IV*** amino-BPs	Established	Occurs in 40% of patients, and mainly after the first infusion
Severe musculoskeletal pain	Still undetermined	Oral BPs	Probable	May occur within days, months or years after initiating a BP treatment
Ocular inflammation	Still undetermined	All BPs	Probable	Often occurs after an acute phase reaction <i>Precipitating factors: rheumatic or pulmonary diseases, IV BPs</i>
Hypocalcaemia	Impairment of the normal compensatory mechanism of parathyroid hormone in response to a decline in the serum calcium <i>Intense calcium uptake into bone</i>	IV > oral BPs	Established	Patient-related risk factors: renal impairment, vitamin D deficiency, limited calcium intake <i>Disease-related risk factors such as massive bone metastases</i> BP-related factors: IV route, high-doses, etc.
Renal toxicity	Still undetermined	Zoledronate and pamidronate	Established	Risk factors for kidney dysfunction: advanced cancer, diabetes mellitus, concomitant nephrotoxic agents <i>BP-related factors: high doses and frequency, etc.</i>
Atypical femoral fragility fractures	Still undetermined	BPs treatment for osteoporosis	Probable	Longer BP treatment (> 5 years), history of low energy fractures, glucocorticoid therapy > six months, active rheumatoid arthritis and low vitamin D levels may increase the risk
Osteonecrosis of the jaw	Still undetermined	IV > oral amino-BPs	Probable	Occurs more frequently in cancer patients who receive high doses of IV BPs with a frequent dosing schedule, than those with osteoporosis <i>Main risk factors: IV form and dentoalveolar procedures</i>

* **BPs**: bisphosphonates ** **GI**: gastrointestinal *** **IV**: intravenous

The first case of severe immune-mediated drug-induced liver injury linked to bisphosphonates was recently described [60]. However, the association between bisphosphonates and liver damage is not quite clear, and the mechanism uncertain. Awaiting further data, bisphosphonates should be carefully administered in patients with preexisting liver disease.

The concern about a potential relationship between bisphosphonate and atrial fibrillation was first related in 2007 in the HORIZON-PFT [61]. This randomized placebo-controlled trial showed that the zoledronate might cause a severe atrial fibrillation. However, clinical trials using bisphosphonates for oncologic bone disease failed to show this link [62]. Accordingly, in November 2008, the FDA declared that no clear association between bisphosphonates and serious or non-serious atrial fibrillation was reported, and recommended that “*healthcare professionals should not alter their prescribing patterns for bisphosphonate medication and the patients should not stop taking their bisphosphonate medication*” [50]. The meta-analyses performed subsequently were also consistent with the FDA’s statement. However, the last one showed a significantly increased risk of serious atrial fibrillation [63]. There is no RCT evidence that risedronate and ibandronate are associated with atrial fibrillation, and postapproval surveillance indicates an incidence < 1/1,000,000 patient-years with risedronate [59]. Until the link between bisphosphonates and atrial fibrillation is clearly established, it is suggested that clinicians should be vigilant in prescribing bisphosphonates for patients with a history of atrial fibrillation or a predisposition to develop atrial fibrillation.

ADDITIONAL SAFETY ISSUE

OPTIMAL DURATION OF BISPHOSPHONATE THERAPY FOR OSTEOPOROSIS AND NEED FOR DRUG HOLIDAY

Osteoporosis is a chronic and progressive disease that requires long-term treatment. The optimal duration of bisphosphonate administration is unclear once treatment extends beyond the duration of placebo-controlled trials. The drug holiday has been proposed because of concerns about increased risk of AFFs with longer duration of bisphosphonate. Moreover, long-term withdrawal extension studies of alendronate, zoledronate and risedronate [17-19, 64] provided clinical evidence that the effect of bisphosphonate therapy was maintained for an unknown length of time following discontinuation of treatment. This is consistent with the prolonged skeletal half-life of bisphosphonates [6].

Although limited data are available to guide practice, an expert panel [65] has recently suggested that bisphosphonate treatment should be continued beyond five years for high-risk patients (T score ≤ -2.5 at hip, previous hip or spine fracture, or ongoing glucocorticoid therapy), and that a drug holiday be considered for moderate-risk patients (T score > -2.5 at hip and no previous spine or hip fracture). The duration for which drug holiday should be advised is not known, because the length of time for

which patients are protected from fracture following discontinuation of bisphosphonate is still unknown. A drug holiday should probably be considered for two to three years, but terminated earlier if the patient sustains fragility fracture. One suggested approach, despite lack of supportive data, is to assess the bone mineral density and measure bone turnover markers about two years after discontinuation, to determine whether treatment should be reinitiated.

Hence, considering the risk of AFF, bisphosphonates should not be withheld from patients at high risk of osteoporotic fracture, because their anti-fracture benefits considerably outweigh their potential for harm [12]. However the safety of this therapy beyond 10 years has not been established yet.

CONCLUSION

The overall safety and tolerability of bisphosphonates are good and serious adverse events are rare. However, their adverse effect profile is still not entirely stated. Practitioners’ awareness of these potential adverse effects can potentially lead to prevent the occurrence of more serious complications due to an earlier detection and management. Until a causal relationship between bisphosphonates and all complications becomes well documented, and the at-risk population defined, physicians must continue to make balanced treatment choices for well-informed patients, to prevent further complications. At the same time, the major therapeutic benefits resulting from the appropriate targeted use of bisphosphonates are not lost as a result of the anxiety concerning rare adverse events such as atypical fracture and osteonecrosis of the jaw.

REFERENCES

1. Eriksen EF, Díez-Pérez A, Boonen S. Update on long-term treatment with bisphosphonates for postmenopausal osteoporosis: a systematic review. *Bone* 2014; 58: 126-35.
2. Kanis JA, McCloskey EV, Johansson H, Cooper C, Rizzoli R, Reginster JY. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. *Osteoporos Int* 2013; 24: 23-57.
3. Bouganim N, Dranitsaris G, Amir E, Clemons M. Optimising the use of bone-targeted agents in patients with metastatic cancers: a practical guide for medical oncologists. *Support Care Cancer* 2011; 19: 1687-96.
4. Whitaker M, Guo J, Kehoe T, Benson G. Bisphosphonates for osteoporosis – Where do we go from here? *N Engl J Med* 2012; 366: 2048-51.
5. Abrahamsen B. Adverse effects of bisphosphonates. *Calcif Tissue Int* 2010; 86: 421-35.
6. Khan SA, Kanis JA, Vasikaran S et al. Elimination and biochemical responses to intravenous alendronate in postmenopausal osteoporosis. *J Bone Miner Res* 1997; 12: 1700-7.
7. Roelofs AJ, Thompson K, Gordon S, Rogers MJ. Molecular mechanisms of action of bisphosphonates: current

- status. *Clin Cancer Res* 2006; 12: 6222s-6230s.
8. Van Beek ER, Cohen LH, Leroy IM et al. Differentiating the mechanisms of antiresorptive action of nitrogen containing bisphosphonates. *Bone* 2003; 33: 805-11.
 9. Russell RG. Bisphosphonates: the first 40 years. *Bone* 2011; 49: 2-19.
 10. Fournier PG, Stresing V, Ebetino FH, Clezardin P. How do bisphosphonates inhibit bone metastasis in vivo? *Neoplasia* 2010; 12: 571-8.
 11. Crandall CJ, Newberry SJ, Diamant A et al. Comparative effectiveness of pharmacologic treatments to prevent fractures: an updated systematic review. *Ann Intern Med* 2014; 161: 711-23.
 12. Suresh E, Pazianas M, Abrahamsem B. Safety issues with bisphosphonate therapy for osteoporosis. *Rheumatology (Oxford)* 2014; 53: 19-31.
 13. MacLean C, Newberry S, Maglione M et al. Systematic review: comparative effectiveness of treatments to prevent fractures in men and women with low bone density or osteoporosis. *Ann Intern Med* 2008; 148: 197-213.
 14. Edwards BJ, Bunta AD, Lane J et al. Bisphosphonates and nonhealing femoral fractures: analysis of the FDA Adverse Event Reporting System (FAERS) and international safety efforts: a systematic review from the Research on Adverse Drug Events And Reports (RADAR) project. *J Bone Joint Surg Am* 2013; 95: 297-307.
 15. Shahinian VB, Kuo YF, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. *N Engl J Med* 2005; 352: 154-64.
 16. Saad F, Adachi JD, Brown JP et al. Cancer treatment-induced bone loss in breast and prostate cancer. *J Clin Oncol* 2008; 26: 5465-76.
 17. Black DM, Schwartz AV, Ensrud KE et al. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. *JAMA* 2006; 296: 2927-38.
 18. Sorensen OH, Crawford GM, Mulder H et al. Long-term efficacy of risedronate: a 5-year placebo-controlled clinical experience. *Bone* 2003; 32: 120-6.
 19. Black DM, Reid IR, Boonen S et al. The effect of 3 versus 6 years of zoledronic acid treatment of osteoporosis: a randomized extension to the HORIZON-Pivotal Fracture Trial (PFT). *J Bone Miner Res* 2012; 27: 243-54.
 20. Coleman RE, McCloskey EV. Bisphosphonates in oncology. *Bone* 2011; 49: 71-6.
 21. McCloskey E, Selby P, Davies M et al. Clodronate reduces vertebral fracture risk in women with postmenopausal or secondary osteoporosis: results of a double-blind, placebo-controlled 3-year study. *J Bone Miner Res* 2004; 19: 728-36.
 22. Zhu I, Zheng Y, Zhou Z. Oral adjuvant clodronate therapy could improve overall survival in early breast cancer: results from an updated systematic review and meta-analysis. *Eur J Cancer* 2013; 49: 2086-92.
 23. Saad F. Clinical benefit of zoledronic acid for the prevention of skeletal complications in advanced prostate cancer. *Clin Prostate Cancer* 2005; 4: 31-7.
 24. Cleland CS, Body JJ, Stopeck A et al. Pain outcomes in patients with advanced breast cancer and bone metastases: results from a randomized, double-blind study of denosumab and zoledronic acid. *Cancer* 2013; 119: 832-8.
 25. Wong M, Pavlakakis N. Optimal management of bone metastases in breast cancer patients. *Breast Cancer (Dove Med Press)* 2011; 3: 35-60.
 26. Cryer B, Bauer DC. Oral bisphosphonates and upper gastrointestinal tract problems: what is the evidence? *Mayo Clin Proc* 2002; 77: 1031-43.
 27. Knopp-Sihota JA, Cummings GG, Homik J, Voaklander D. The association between serious upper gastrointestinal bleeding and incident bisphosphonate use: a population-based nested cohort study. *BMC Geriatr* 2013; 13: 36.
 28. Olson K, Van Poznak C. Significance and impact of bisphosphonate-induced acute phase responses. *J Oncol Pharm Pract* 2007; 13: 223-9.
 29. Reid IR, Gamble GD, Mesenbrink P et al. Characterization of and risk factors for the acute-phase response after zoledronic acid. *J Clin Endocrinol Metab* 2010; 95: 4380-7.
 30. Miller PD, McClung MR, Macovei L et al. Monthly oral ibandronate therapy in postmenopausal osteoporosis: 1-year results from the MOBILE study. *J Bone Miner Res* 2005; 20: 1315-22.
 31. Food and Drug Administration. Severe pain with osteoporosis drugs. 2008. <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/psn/transcript.cfm?show=73>. Accessed September 2014.
 32. [No authors listed]. Bisphosphonates: bone, muscle and joint pain. *Prescrire Int* 2009; 18: 23.
 33. Wysowski DK, Chang JT. Alendronate and risedronate: reports of severe bone, joint, and muscle pain. *Arch Intern Med* 2005; 165: 346-7.
 34. Demonaco HJ. Patient- and physician-oriented web sites and drug surveillance: bisphosphonates and severe bone, joint, and muscle pain. *Arch Intern Med* 2009; 169: 1164-6.
 35. Osta LE, Osta BE. Acute blepharitis: an unusual complication of zoledronic acid. *Int J Rheum Dis* 2015 Sep 10. doi: 10.1111/1756-185X.12743 [Epub ahead of print]
 36. Pazianas M, Clark EM, Eiken PA, Brixen K, Abrahamson B. Inflammatory eye reactions in patients treated with bisphosphonates and other osteoporosis medications: cohort analysis using a national prescription database. *J Bone Miner Res* 2013; 28: 455-63.
 37. Tanvetyanon T, Stiff PJ. Management of the adverse effects associated with intravenous bisphosphonates. *Ann Oncol* 2006; 17: 897-907.
 38. Chennuru S, Koduri J, Baumann MA. Risk factors for symptomatic hypocalcaemia complicating treatment with zoledronic acid. *Intern Med J* 2008; 38: 635-7.
 39. Patel K, Brahmabhatt V, Ramu V. Zoledronic acid-induced severe hypocalcaemia in a prostate cancer patient with extensive osteoblastic bone metastases. *Tenn Med* 2005; 98: 83-5, 89.
 40. Bounameaux HM, Schifferli J, Montani JP, Jung A, Chatelant F. Renal failure associated with intravenous diphosphonates. *Lancet* 1983; 1: 471.
 41. Bergner R, Diel IJ, Henrich D, Hoffmann M, Uppenkamp M. Differences in nephrotoxicity of intravenous bisphosphonates for the treatment of malignancy-related bone disease. *Onkologie* 2006; 29: 534-40.
 42. Pecherstorfer M, Rivkin S, Body JJ, Diel I, Bergström B. Long-term safety of intravenous ibandronate for up to 4 years in metastatic breast cancer: an open-label trial. *Clin Drug Investig* 2006; 26: 315-22.
 43. Rosen LS, Gordon D, Kaminski M et al. Zoledronic acid versus pamidronate in the treatment of skeletal metastases in patients with breast cancer or osteolytic lesions

- of multiple myeloma: a phase III, double-blind, comparative trial. *Cancer J* 2001; 7: 377-87.
44. Miller PD, Jamal SA, Evenepoel P, Eastell R, Boonen S. Renal safety in patients treated with bisphosphonates for osteoporosis: a review. *J Bone Miner Res* 2013; 28: 2049-59.
 45. Odvina CV, Zerwekh JE, Rao DS, Maalouf N, Gottschalk FA, Pak CY. Severely suppressed bone turnover: a potential complication of alendronate therapy. *J Clin Endocrinol Metab* 2005; 90: 1294-301.
 46. Shane E, Burr D, Abrahamsen B et al. Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res* 2014; 29: 1-23.
 47. Girgis CM, Sher D, Seibel MJ. Atypical femoral fractures and bisphosphonate use. *N Engl J Med* 2010; 362: 1848-49.
 48. Saleh A, Hegde VV, Potty AG, Lane JM. Bisphosphonate therapy and atypical fractures. *Orthop Clin North Am* 2013; 44: 137-51.
 49. Black DM, Kelly MP, Genant HK et al. Bisphosphonates and fractures of the subtrochanteric or diaphyseal femur. *N Engl J Med* 2010; 362: 1761-71.
 50. Food and Drug Administration. Information on bisphosphonates. 2008. Accessed September 2014. <http://www.fda.gov/Drugs/DrugSafety/Default.htm>
 51. El Osta L, El Osta B, Lakiss S, Hennequin M, El Osta N. Bisphosphonate-related osteonecrosis of the jaw: awareness and level of knowledge of Lebanese physicians. *Support Care Cancer* 2015; 23: 2825-31.
 52. 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. *Aust Endod J* 2009; 35: 119-30.
 53. Köhl S, Walter C, Acham S, Pfeffer R, Lambrecht JT. Bisphosphonate-related osteonecrosis of the jaws .a review. *Oral Oncol* 2012; 48: 938-47.
 54. Compston J. Pathophysiology of atypical femoral fractures and osteonecrosis of the jaw. *Osteoporos Int* 2011; 22: 2951-61.
 55. Khosla S, Burr D, Cauley J et al. Bisphosphonate-associated osteonecrosis of jaw: report of a task force of the American Society of Bone and Mineral Research. *J Bone Miner Res* 2007; 22: 1479-91.
 56. Dickinson M, Prince HM, Kirsa S et al. Osteonecrosis of the jaw complicating bisphosphonate treatment for bone disease in multiple myeloma: an overview with recommendations for prevention and treatment. *Intern Med J* 2009; 39: 304-16.
 57. Sun K, Liu JM, Sun HX, Lu N, Ning G. Bisphosphonate treatment and risk of esophageal cancer: a meta-analysis of observational studies. *Osteoporos Int* 2013; 24: 279-86.
 58. Vinogradova Y, Coupland C, Hippisley-Cox J. Exposure to bisphosphonates and risk of gastrointestinal cancers: series of nested case-control studies with QResearch and CPRD data. *BMJ* 2013; 346: f114.
 59. Rizzoli R, Reginster JY, Boonen S et al. Adverse reactions and drug-drug interactions in the management of women with postmenopausal osteoporosis. *Calcif Tissue Int* 2011; 89: 91-104.
 60. Goossens N, Spahr L, Rubbia-Brandt L. Severe immune-mediated drug-induced liver injury linked to ibandronate: A case report. *J Hepatol* 2013; 59: 1139-42.
 61. Black DM, Delmas PD, Eastell R et al. HORIZON Pivotal Fracture Trial. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med* 2007; 356: 1809-22.
 62. Rosen LS, Gordon D, Tchekmedyian S et al. Zoledronic acid versus placebo in the treatment of skeletal metastases in patients with lung cancer and other solid tumors: a phase III, double-blind, randomized trial – the Zoledronic Acid Lung Cancer and Other Solid Tumors Study Group. *J Clin Oncol* 2003; 21: 3150-7.
 63. Sharma A, Chatterjee S, Arbab-Zadeh A et al. Risk of serious atrial fibrillation and stroke with use of bisphosphonates: Evidence from a meta-analysis. *Chest* 2013; 144: 1311-22.
 64. Watts NB, Chines A, Olszynski WP et al. Fracture risk remains reduced one year after discontinuation of risendronate. *Osteoporos Int* 2008; 19: 365-72.
 65. McClung M, Harris ST, Miller PD et al. Bisphosphonate therapy for osteoporosis: benefits, risks and drug holiday. *Am J Med* 2013; 126: 13-20.