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Long-term Safety Concerns of Antiresorptive Therapy

Jie Zhang, PhD^a, Kenneth G. Saag, MD, MSc^b, and Jeffrey R. Curtis, MD, MS, MPH^{c,*}

^aHealth Services/Comparative Effectiveness Research Training Program, Department of Epidemiology, University of Alabama at Birmingham, 1665 University Boulevard, RPHB 517B, Birmingham, AL 35294, USA

^bDivision of Clinical Immunology & Rheumatology, University of Alabama at Birmingham, Faculty Office Tower 820, 510 20th Street South, Birmingham, AL 35294, USA

^cDivision of Clinical Immunology & Rheumatology, University of Alabama at Birmingham, Faculty Office Tower 805D, 510 20th Street South, Birmingham, AL 35294, USA

Abstract

Bisphosphonates prevent the loss of bone mineral content by inhibiting bone resorption. As a result, bone turnover is decreased and bone mineral density maintained or even increased. Currently, bisphosphonates account for approximately 80% of all medications prescribed for osteoporosis.¹ Although these medications were well tolerated and safe during large-scale clinical trials, several rare and potentially serious adverse events are reported to be associated with long-term bisphosphonate use from postmarketing reports and epidemiologic studies. These adverse events include osteonecrosis of the jaw (ONJ), atypical fractures, and esophageal cancer. This review summarizes studies examining the association between long-term bisphosphonate use and these adverse outcomes.

Keywords

Osteoporosis; Anti-resorptive therapy; Safety concerns

Bisphosphonate-Related Osteonecrosis of the Jaw

Putative Pathogenesis

ONJ affects the maxilla and the mandible, with the defining symptom of prolonged exposed mandibular and/or maxillary bone, after an insult to the jaw, leading to an oral lesion with delayed healing. Historically, from the mid-1880s until the 1900s, jaw osteonecrosis, known as phossy jaws, symptomatically resembled ONJ cases associated with bisphosphonate use and was once epidemic among workers of the match industry due to occupational exposure to high level of phosphorous fume.² Before ONJ was associated with bisphosphonate use, it was primarily associated with radiation to the head and neck for cancer treatment.

The pathogenesis of so-called bisphosphonate-related ONJ is not clear and has been hypothesized to involve multiple processes. It has been postulated that reduced bone remodeling associated with bisphosphonate use may lead to an increased risk of developing bone necrosis in select patients. Also, the antiangiogenic effects of bisphosphonates may result in a reduction in the blood supply to the region and contribute to poor wound healing. In addition, infection has also been implicated in the pathogenesis of ONJ.³

Case Series and Clinical Features of ONJ

Two case series reported in 2003 and 2004 first suggested an association between bisphosphonate use and ONJ.^{3–5} Marx⁴ described 36 cases of painful exposed bone in the maxilla and/or mandible; all of the cases used bisphosphonates and most of them for cancer treatment (n 5 35). They also described several key clinical features of ONJ, including disproportionately affecting the mandibular bone (81%), most cases (78%) developing after dental extraction, and cases refractory to treatment. Similarly, Ruggiero and colleagues⁵ conducted a medical record review of 63 ONJ cases. All of their cases had either a history of cancer or osteoporosis and all of them had used bisphosphonate (56 cases were cancer patients exposed to intravenous bisphosphonates). After these case series, many case reports and case series, mainly among cancer patients, of bisphosphonate-associated ONJ were published.^{6,7} These reports further characterized ONJ cases and identified several putative risk factors for ONJ, including greater length and cumulative dose of bisphosphonate use; presence of invasive dental procedures, such as extraction and implant; comorbidities; alcohol and tobacco use; and pre-existing periodontal disease. In a majority of ONJ cases, infection was present. Other common symptoms include bone pain, swelling, paresthesia, purulent discharge, and loosening of teeth. A small proportion of these cases were asymptomatic.

Few of these case series included ONJ patients receiving bisphosphonates for osteoporosis but mostly for malignancy. A case series from Italy, including patients with both indications (24 osteoporosis patients and 78 cancer patients), reported that the oral lesions were generally less severe in osteoporosis patients than in cancer patients with bisphosphonate-related ONJ.⁸ Another institution-based case series at the University of Southern California identified 9 ONJ cases treated with oral bisphosphonate for osteoporosis. Among these cases, the age ranged from 63 or 80 years and all were preceded by tooth extraction or denture trauma. One significant finding was that the duration of oral bisphosphonate use (70 mg of alendronate per week) in 2 of the 9 ONJ cases was as short as 12 months, suggesting that even short-term exposure could increase the risk of ONJ.⁹

Case Definition of ONJ

The American Academy of Oral and Maxillofacial Surgeons (AAOMS) proposed a definition for bisphosphonate-related ONJ that requires the satisfaction of the following criteria: (1) current or prior use of bisphosphonate, (2) an area of exposed bone within the maxillofacial region without healing for more than 8 weeks, and (3) absence of history of radiation to the jaws.⁶ The AAOMS further proposed staging criteria that categorized patients into 1 of 4 stages and recommended stage-specific treatment strategies. The 4 stages were patients with asymptomatic necrotic bone (stage 1); patients with necrotic bone

accompanied by infection with or without purulent drainage (stage 2); and patients with necrotic bone accompanied by infection, pain, and at least one of the conditions, including pathologic fractures, extraoral fistula, or osteolysis extending to the inferior border (stage 3).⁶

The case definition of bisphosphonate-associated ONJ developed by the American Society for Bone and Mineral Research (ASBMR) task force was similar except that in cases when the duration of unhealed lesion was less than 8 weeks, the cases should be defined as “suspected” cases and should be followed-up to determine whether they are indeed ONJ cases. To aid the diagnosis of ONJ cases, the task force provided a list of differential diagnosis to be ruled out, such as periodontal disease, gingivitis or mucositis, and infectious osteomyelitis.⁷ Such case definition is problematic because the exposure (bisphosphonate use) is part of the case definition.

Epidemiology of ONJ (Frequency of Occurrence)

When discussing the incidence or prevalence of ONJ cases, it is important to define the at-risk population because ONJ has been reported far more frequently in patients treated for cancer than for osteoporosis. Other considerations include the definition of the outcome because surrogate outcomes other than ONJ were used in some studies, and the methods used to define the at risk population and to ascertain ONJ cases were highly variable.

The incidence of ONJ among cancer patients has been estimated to range from 2% to 6%.^{10–12} From the database of myeloma patients at the University of Maryland (n 5 340), 11 (3% of myeloma patients) ONJ cases were identified.¹² At the University of Texas MD Anderson Cancer Center, a chart review of 3994 patients treated with intravenous bisphosphonate was conducted and 29 ONJ cases were identified among patients with breast cancer (n 5 16) and myeloma (n 5 13), resulting in incidence proportions of 1.2% and 2.4%, respectively.¹⁰ In a population-based study using linked data from the Surveillance, Epidemiology and End Results (SEER) Program and Medicare, a 6-year cumulative incidence rate of 5.5% for jaw or facial surgery or a diagnosis of inflammatory conditions of osteomyelitis of the jaw was reported among all cancer patients.¹¹ A limitation of the study was that surrogate outcomes (oral surgery or inflammatory conditions of osteomyelitis of the jaw) were used rather than a clinical ONJ case definition.

The occurrence of ONJ in patients receiving bisphosphonate for osteoporosis is rare. Several epidemiologic studies have generated prevalence estimates ranging from 1 to 20 per 1000.^{13–15} In a study conducted in Australia and New Zealand, oral and maxillofacial surgeons in the two countries were surveyed to identify ONJ cases treated with bisphosphonate and the total number of bisphosphonate users estimated using various prescription databases was used as the denominator. When patients treated with bisphosphonates for reasons other than osteoporosis were excluded, there were 36 ONJ cases and the prevalence of ONJ among them was estimated at between 1 and 4 per 1000. The corresponding estimates were 10 times higher among those who had dental extraction.¹³ In another study conducted within a large health care plan in the United States, oral bisphosphonate users identified based on pharmacy claims were surveyed with regard to ONJ symptoms. A total of 9 ONJ cases were confirmed and the prevalence of ONJ was

estimated at between 5 and 20 per 1000.¹⁴ Finally, in a study conducted by Fellows and colleagues,¹⁵ 6 ONJ cases were ascertained among 21,163 oral bisphosphonate users, resulting in a prevalence of 3 per 1000.

Although rare, ONJ cases may occur in individuals not exposed to bisphosphonate. Among enrollees of two large health maintenance organizations that were part of the Dental Practice-Based Research Network, ONJ cases were ascertained using a 5-step process that incorporated review of diagnosis and procedure codes, electronic medical records and medical charts, and survey of patients, dentists, and oral surgeons. Among a total of 572,606 eligible enrollees, including those with and without presumed ONJ risk factors, a total of 23 confirmed ONJ cases were identified, resulting in an incidence rate of 0.63 (95% CI, 0.39–1.59) per 100,000 person-years.¹⁵ Of the 23 cases, 6 occurred among oral bisphosphonate user, 2 among intravenous (IV) bisphosphonate users, 12 among cancer patients, 4 among patients with history of head and neck radiation, and 3 among patients free of any risk factors (the categories are not mutually exclusive; other risk factors examined included osteoporosis, osteopenia, diabetes, and immune disorders).¹⁵

Controlled Studies of the Independent Association Between Oral Bisphosphonate Use and ONJ

The association between oral bisphosphonate use and ONJ has been examined in a few controlled studies, most of them reporting a positive association. Etminan and colleagues¹⁶ conducted a nested case-control study using administrative data from Canada to examine the association between oral bisphosphonate use and nonspecific aseptic osteonecrosis (*International Classification of Diseases, Ninth Revision [ICD-9] code 733.4*). A total of 196 cases were identified using *ICD-9* diagnosis code and controls were selected to match the cases on age, calendar time, and length of follow-up. Bisphosphonate use in the previous year before ONJ diagnosis was examined. Both current and past oral bisphosphonate use (alendronate, etidronate, and risedronate) were associated with increased risk of aseptic osteonecrosis (odds ratio [OR] 2.9; 95% CI, 1.7–5.1) for bisphosphonate users compared with nonusers.¹⁶ A limitation of the study was that it was conducted before the *ICD-9* code for ONJ was introduced and, as a result, the cases identified were not site-specific.

The association between bisphosphonate for osteoporosis and ONJ, not a surrogate outcome, was examined in two epidemiologic studies conducted using the Dental Practice-Based Research Networks. In the case-control study, ONJ was defined as exposed necrotic bone in the maxilla or mandible regardless of duration or potential cause in patients without history of facial trauma. Practitioners inside and out of the network were contacted and 308 ONJ cases were identified. Of these ONJ cases, 191 agreed to participate in the study and 573 controls were selected from the same practices from which the cases came. After excluding patients with a history of cancer regardless of the site, bisphosphonate use was associated with ONJ and a dose-response was observed between the magnitude of the association and duration of bisphosphonate use. The OR and 95% CI among those with fewer than 2 years, 2 to 5 years, and more than 5 years of bisphosphonate were 5.2 (1.2–22.5), 11.4 (3.2–40.2), and 26.6 (5.3–133.6).¹⁷ In the cohort study, ONJ cases were defined as exposed necrotic lesion in the maxilla or mandible that were confirmed by manual chart review and were

systemically ascertained among enrollees of two large health maintenance organizations. Oral bisphosphonate use and osteoporosis diagnosis were both associated with increased odds of having ONJ ORs of 14.9 and 10.3, respectively.¹⁵ In addition to osteoporosis and oral bisphosphonate use, cancer diagnosis, radiation at head and neck, and glucocorticoid exposure were found to be risk factors of ONJ.

Section Summary

The occurrence of ONJ is rare in the general population. Bisphosphonate use in cancer patients seems associated with a significant increase in the risk of developing ONJ; increasing evidence suggests that bisphosphonate use for osteoporosis may also be associated an increased ONJ risk, although the magnitude of the absolute risk of ONJ in osteoporosis patients is low. Several professional societies, including ASBMR, AAOMS, and the American Dental Association, have made recommendations with regard to patient dental care in patients initiating or receiving bisphosphonate therapy.¹⁸ Both ASBMR and AAOMS recommended that when possible, comprehensive dental examination and invasive dental procedures should be performed before initiating intravenous bisphosphonate therapy for cancer treatment. ASBMR does not specifically recommend such precaution, however, in patients initiating bisphosphonate for osteoporosis or Paget disease.¹⁸

Atypical Subtrochanteric and Diaphyseal Fractures

Putative Pathogenesis

Safety concerns that long-term bisphosphonate use may adversely affect the repair of microdamage is not new. At least in theory, bisphosphonate may alter the biomechanical properties of bone matrix via its effect on bone collagen and bone mineralization density distribution, resulting in brittle and stiff bones that could fracture with little trauma. Reduced bone remodeling, coupled with the antiangiogenic effect of bisphosphonates, may further impair the healing of stress fractures, which eventually develop into a complete fracture. The putative mechanisms and preclinical studies suggestive of possible mechanisms have been reviewed elsewhere in detail.¹⁹

Case Series and Clinical Features of Atypical Subtrochanteric and Diaphyseal Fractures

The case series reported by Odvina and colleagues²⁰ in 2005 first linked long-term bisphosphonate use with low-energy subtrochanteric and diaphyseal fractures. Among a series of 9 patients who had nonspinal fracture while on long-term alendronate therapy, 3 of them had a fracture at the femoral shaft. After the publication of this case series, Lenart and colleagues,²¹ in a letter to *The New England Journal of Medicine*, reported 15 cases of postmenopausal women with low-energy subtrochanteric or diaphyseal fractures. The radiographic features of a transverse or oblique pattern with beaking of the cortex and cortical thickening were present in 10 of these patients and these 10 patients had significantly longer duration of alendronate use (7.3 vs 2.8 years, $P < .0001$). In a similar case series of 17 patients who had low-energy subtrochanteric fractures while on alendronate therapy, similar radiographic features were observed.²² Yet in another retrospective case series, radiographs of 152 femur fractures were reviewed and 20 were determined to have the defining features of atypical fracture on radiograph. Among the 20 subjects, 15 were

receiving alendronate with mean treatment duration of 5 years and 2 were receiving risidronate with mean duration of 3 years. In contrast, only 2 patients were taking alendronate and 1 residronate among the 132 patients without the defining radiographic features.²³

Several clinical features and potential risk factors associated with increased risk of atypical subtrochanteric and diaphyseal fractures have been suggested by the case series, including concomitant glucocorticoid therapy,^{20,23} prodromal pain and discomfort,^{22,24} low serum 25-hydroxyvitamin D,²³ increased tendency to be bilateral,²² delayed fracture healing,²⁰ and stress reaction.²²

Case Definition of Atypical Subtrochanteric and Diaphyseal Fractures

A provisional case definition was developed by the ASBMR task force for atypical subtrochanteric and diaphyseal fractures.¹⁹ The case definition includes several major and minor features and to qualify for a case, all major features are required to be present, including occurring anywhere along the femoral diaphysis distal to the less trochanter, no or minimal trauma, transverse or short oblique pattern, noncomminuted, and beaking of the cortex.¹⁹ Examples of the minor features are thickened diaphyseal cortices, prodromal symptoms, and bilateral patterns.¹⁹

Epidemiology of Subtrochanteric and Diaphyseal Fractures (Frequency of Occurrence)

Currently, the incidence or prevalence of atypical subtrochanteric and femoral shaft fractures is unknown because identification of these fractures requires examination of radiographs to determine the presence or absence of the atypical features (discussed previously). To identify any subtrochanteric or femoral shaft fracture, several studies have used administrative data to examine the frequency of occurrence of these fractures regardless of atypical radiographic features. It was estimated that fractures occurring in this region accounted for approximately 4% to 8% of all hip fractures.^{25,26} Wang and Bhattacharyya²⁵ found that although the overall hip fracture incidence has decreased from 1996 to 2007 for both women and men by 32% and 21%, respectively, the incidence of subtrochanteric fractures remained stable among men and increased among women. In another study in which data from National Hospital Discharge Survey (1996–2006) and Market Scan (2002–2006) were examined, the rates of subtrochanteric and femoral shaft fracture remained unchanged over time.²⁶ Only a small proportion of these subtrochanteric fractures, however, are likely considered atypical based on radiographic features required for the case definition. For example, in a study in which radiographs for more than 600 femur fractures were reviewed, the characteristic radiographic features of atypical fractures were present only in 102 patients.²⁷ In another study, using *ICD, Tenth Revision (ICD-10)* code, 1271 patients were identified as having sustained a subtrochanteric or femoral shaft fracture. After reviewing the radiographs of 1234 patients, however, only 59 (4.8%) of these fractures were classified as atypical.²⁸

Controlled Studies of the Independent Association Between Oral Bisphosphonate Use and Atypical Subtrochanteric or Diaphyseal Fracture

The association between bisphosphonate use and subtrochanteric or diaphyseal fractures was examined in several controlled epidemiologic studies and somewhat conflicting results have been reported. Based on data from the Danish National Hospital Discharge Register and the National Prescription Database, subjects who sustained a typical hip, subtrochanteric, or diaphyseal fracture were identified and the distributions of demographic characteristics, alendronate use in the previous year, and level of trauma associated with the fractures were similar across the 3 groups. Using those data, Abrahamsen and colleagues²⁹ conducted a cohort study and found that the risks of developing a typical hip, subtrochanteric, or femoral shaft fracture were all elevated among alendronate users to a similar extent. Of particular interest, high adherence was associated with reductions in fractures risk across 3 types of fractures, suggesting that the occurrence of fractures at all 3 locations was potentially driven by underlying osteoporosis. Similarly, no association was found in an investigation using data from 3 large randomized trials of oral alendronate and zoledronate totaling 14,195 women. During follow-up, 12 subtrochanteric and diaphyseal fractures based on radiographic report were identified and no association was found between bisphosphonate use and these fractures (hazard ratios [HRs] and 95% CIs were 1.03 [0.06–1.65], 1.33 [0.12–14.7], and 1.51 [0.25–9.00] for each respective trial).³⁰ Consistent with the 2 reports, the risks of developing subtrochanteric or diaphyseal fractures were similar (HR 1.0; 95% CI, 0.7–1.5) between bisphosphonate and calcitonin/raloxifene users in a recent cohort study conducted among Medicare beneficiaries with supplemental assistance in Pennsylvania and New Jersey from 1996 to 2006. When the analysis was restricted to those treated with bisphosphonate for longer than 5 years, the estimate suggested a nonsignificantly increased risk (HR 2.02; 95% CI, 0.41–10.00).³¹

In contrast to the studies described above, a significant association between bisphosphonate use and subtrochanteric or diaphyseal fractures has been reported in other controlled observational studies. In a retrospective case-control study, cases consisted of postmenopausal women who had a low-energy subtrochanteric or diaphyseal fracture between 2000 and 2007 and patients with low-energy intertrochanteric or femoral neck fractures during the same time period matched by age, body mass index, and race were selected as controls. Cases were more likely to be bisphosphonate users compared with controls (27% vs 11%). When fractures cases were divided into 2 groups, depending on whether the radiographic features of cortical thickening and beaking of the cortex were present or absent, those with these features were more likely to have used bisphosphonate for longer term (mean duration of bisphosphonate use 7.3 vs 2.8 years).³² A more recent nested case-control study was conducted using administrative data from Canada.³³ The study found that long-term (≥5 years, adjusted OR 2.74, 95% CI 1.25–6.02) bisphosphonate use was associated with increased risk of subtrochanteric and femoral shaft fracture. The association was not present among those with shorter duration of bisphosphonate use (adjusted OR 0.90; 95% CI, 0.48–1.68) and was increased but not statistically significant among those with 3 to 5 years of medication use (adjusted OR 1.59; 95% CI, 0.80–3.15). When typical femoral neck fracture was examined, a trend in the opposite direction was found that longer duration of bisphosphonate use was associated with decreased fracture

risk. As part of the study, the investigators evaluated the validity of the *ICD-10* diagnosis codes and reported a positive predictive value and a sensitivity of 91% and 81% to correctly identify the location of fracture (although not atypical radiographic features) after reviewing a total of 2077 charts.³³ The association between bisphosphonate use and atypical fracture was confirmed yet in another recent population-based study conducted in Sweden. In the study, radiographs from women 55 years of age or older who sustained femur fractures in 2008 were reviewed to ascertain atypical features.²⁸ The relative risk (RR) of atypical fracture associated with bisphosphonate use was 47.3; however, perhaps more importantly, the increase in absolute risk was only 5 per 10,000 person-years. Of particular interest, the study reported that the risk of atypical fracture decreased rapidly after discontinuation of bisphosphonate therapy in contrast to its long-lasting protective effect. The study estimated that the risk of atypical fracture decreased by 70% annually after discontinuation and that the crude incidence among those who last used bisphosphonate 1 to 2 years ago was 0.1 per 10,000 person-year, only slightly above that among those who never used bisphosphonate (crude incidence 0.09 per 10,000 person-years).

Section Summary

Case reports and series initially suggested an association between bisphosphonate use and atypical subtrochanteric and femoral shaft fractures and led to the identification of unique radiographic features that define these fractures. Despite conflicting results reported from epidemiologic studies, increasing evidence suggests an elevated fracture risk in long-term bisphosphonate users (5 years or more). The magnitude of the association between bisphosphonate use and the occurrence of these fractures, however, remains unclear because many of the population-based epidemiologic studies relied on diagnosis codes (*ICD-9* or *ICD-10*) to identify fracture cases based on the location and not the atypical and more specific radiographic features.^{29,31,33} In addition, lack of precision in risk estimates was a major limitation in several of these studies due to the small number of atypical fracture cases identified.^{30,31}

With increasing evidence pointing to an association between these atypical fractures and long-term bisphosphonate use of 5 years or more, the US Food and Drug Administration issued a warning regarding the possible risk of atypical subtrochanteric and femoral shaft fractures in patients with long-term bisphosphonate use for the prevention and treatment of osteoporosis. The mandated labeling change affected alendronate, risedronate, ibandronate, and zoledronic acid.

Esophageal Cancer

Putative Pathogenesis

Esophageal and gastrointestinal events are the most frequent adverse events that were observed during trials of oral bisphosphonate for osteoporosis. Most of these reports have been nonulcer dyspepsia and reflux type symptoms. More serious esophageal problems have also been described. In a clinical trial of oral preparations of pamidronate for patients with Paget disease, 5 patients receiving two different preparations of oral pamidronate developed erosive esophagitis.³⁴ A case report of a 59-year-old obese woman developing ulcerative

esophagitis within 7 days of initiating oral alendronate for osteoporosis was followed by several case series of 15 patients with alendronate-associated esophagitis.^{35–37} In addition, one case report described a 70-year-old man who developed esophageal perforation after 3 months of oral alendronate treatment for glucocorticoid-induced osteoporosis.³⁸

Case Series of Esophageal Cancer

Given the biologic plausibility of a causal association between bisphosphonates and esophageal pathology, in a letter to *The New England Journal of Medicine*, a Food and Drug Administration investigator described a total of 23 cases of esophageal cancer after alendronate use received between 1995 and 2008. The median duration of alendronate use to diagnosis was 2.1 years and Barrett esophagus was reported in 1 patient. The same letter described another 31 cases of esophageal cancer reported in Europe and Japan among bisphosphonate users. The median time on bisphosphonate therapy until diagnosis was 1.3 years and Barrett esophagus was reported in 3 patients.³⁹

Epidemiology of Esophageal Cancer (Frequency of Occurrence)

Rapid increase in the incidence of esophageal cancer since the 1970s has been observed in a several studies in the United States.^{40–42} Although the exact mechanism is not known, this increase was in parallel with the rising prevalence of obesity, which may lead to higher intra-abdominal pressure and reflux disease. Using data from the Surveillance Epidemiology and End Results, Pohl and colleagues⁴⁰ estimated that the annual incidence of esophageal cancer increased 7-fold from 3.6 per a million in 1973 to 25.6 per a million 2006. The incidence rates of esophageal cancer were compared among oral bisphosphonate users, users of other anti-osteoporosis medications, and SEER rates. The incidence rate of esophageal cancer was not increased among oral bisphosphonate users compared with those taking other osteoporosis medications (incidence rate ratio [IRR] 0.6; 95% CI, 0.1–4.7) or the SEER rate (IRR, 1.1; 95% CI, 0.3, 4.8).⁴³

Controlled Studies of the Association Between Oral Bisphosphonate Use and Esophageal Cancer

Since the case series report, several controlled studies were conducted to assess the association between bisphosphonate use and esophageal and gastric cancer. Using data from Danish national registers, oral bisphosphonate use was found protective of esophageal cancer.⁴⁴ These studies were reported, however, in the format of letters to the editor and detailed information regarding methods of the study was not available for evaluation.

Using data from the UK General Practice Research Database, both a matched cohort study and a separate case-control study were conducted to examine the association between bisphosphonate use and esophageal cancer and conflicting results were reported.^{45,46} In the matched cohort study, all new users of bisphosphonate were identified; and for each bisphosphonate user, a gender-matched, age-matched, and practiced-matched control was identified regardless of bisphosphonate use. The incidences of esophageal and gastric cancer were compared and bisphosphonate use was not associated with an increased incidence for either cancer type.⁴⁵ In addition, no association was found in stratified analyses by cumulative bisphosphonate use and by subtypes of bisphosphonate.⁴⁵

In contrast, a case-control study by Green and colleagues,⁴⁶ using the same data source, found increased risk of esophageal cancer among oral bisphosphonate users (RR 1.30; 95% CI, 1.02–1.66). When bisphosphonate users were stratified by number of prescriptions (<9 or ≥9) and by duration of use (≤1 year, 1–3 years, and ≥3 years), increased risk was observed only among those who had 10 or more prescriptions (RR 1.93; 95% CI, 1.37–2.70) and not among those who used 9 prescriptions or less (RR 0.98, 95% CI, 0.66–1.31). A dose-response was observed by duration of use that the RRs were 0.98, 1.12, and 2.24 among those who used for no more than a year, 1 to 3 years, and 3 years or more.⁴⁶ The results from these two studies cannot be directly compared due to different study designs (case-control vs matched cohort) and different methods used to ascertain esophageal cancer cases, and dissimilar comparator groups. For example, in the matched-cohort study, bisphosphonate users were eligible to be included in the control cohort and, once included, they were removed from the bisphosphonate cohort.

To further ascertain the independent association between bisphosphonate and esophageal cancer, a cohort of patients with Barrett esophagus was identified from the National Veterans Affairs Databases from the Veterans Affairs from 2000 to 2009. Among these patients, incident esophageal cancer cases were identified and controls were sampled using incident density sampling matching on age and date of diagnosis for Barrett's esophagus at a ratio of 1:6. In this population of mostly men (97%), no association was found between bisphosphonate use and esophageal cancer (adjusted OR 0.92; 95% CI, 0.21–4.15).⁴⁷

Section Summary

The biologic plausibility of a causal association between oral bisphosphonate and esophageal cancer, and several case series have raised further questions about whether long-term bisphosphonate use is associated with increased risk of esophageal cancer. Currently, conflicting results are reported from epidemiologic studies that provide only limited evidence either way. Nevertheless, these reports should prompt physicians to ask patients to report early signs and symptoms of esophageal complications that may merit further investigation or closer surveillance.

Risk Versus Benefit

Despite the uncertainties regarding the associations between bisphosphonate use and these potential serious adverse events, these events have been highly publicized in popular media and high-profile publications. Furthermore, based on these reports, physicians may be deterred from prescribing bisphosphonates for at least the short-term treatment of osteoporosis, a condition that remains currently undertreated. For example, if it is assumed that the 5-year exposure to bisphosphonates doubled the risk of subtrochanteric and diaphyseal fractures and were associated with a 36% reduction in the risk of typical hip fractures and that an annual risk of all hip fractures among postmenopausal women was 1%, for every 10,000 patients at high risk of fracture, bisphosphonate use would prevent 108 hip fractures and cause 3 additional subtrochanteric and diaphyseal fractures.⁴⁸ This calculation demonstrates that the benefits of bisphosphonate treatment, at least in the short term, outweigh the risks of subtrochanteric and diaphyseal fractures. This analysis, however, is based on imperfect data and uncertainty about the magnitude of the association between

bisphosphonate use and these potential adverse outcomes that may increase with cumulative bisphosphonate use.

Drug Holiday

An important clinical implication of these potential adverse events from long-term bisphosphonate use pertains to the question of what is the optimal length of treatment with these agents. Data on potential bisphosphonates adverse effects also should be coupled with evidence that these agents continue exerting a suppressive effect on bone resorption long after they have been discontinued. Data from extensions to two large clinical trials with up to 10 years of follow-up showed that although long-term treatment with bisphosphonate of up to 10 years continued to yield beneficial effect with regard to bone density, patients who discontinued bisphosphonate continued to experience beneficial effect of up to 5 years.^{47,49,50} At the completion of the Fracture Intervention Trial, 1099 participants treated with oral alendronate for 5 years in the trial were further randomized to alendronate or placebo for another 5 years. The study showed that an additional 5 years of treatment was not associated with a significantly decreased risk of nonvertebral fractures (RR 1.00; 95% CI, 0.76–1.32) or morphometric vertebral fractures (RR 0.86; 95% CI, 0.60–1.22). The investigators observed a decreased risk of clinical vertebral fractures (RR 0.45; 95% CI, 0.24–0.85) with an absolute risk reduction of 2.9% over 5 years.⁴⁹ In a posthoc analysis, they found that risk reduction for hip fracture was present among those with femoral neck T score less than -2.5.⁵¹ In the 6-year to 10-year extension of another trial of oral alendronate in postmenopausal women with osteoporosis, those who were treated with 20 mg per day for 2 years and 5 mg per day for 3 years were assigned to placebo, and at year 10, the bone mineral density at lumbar spine, trochanter, total hip, and total body remained above baseline level.⁵⁰ In addition to the data from the two trials of alendronate, it has been demonstrated that after treatment was discontinued after 3 continuous years of treatment with risedronate, the antifracture effect remained for the fourth year and that those treated had a significant lower incidence of morphometric vertebral fracture rates.⁵²

In another study using administrative claims data, among subjects who have used bisphosphonate for 2 years with at least moderate compliance to treatment (medication possession ratio >66%), the risk of a subsequent hip fracture was found to increase approximately one year after discontinuation.⁵³ No significant difference was observed, however, among those more compliant or with a longer duration of bisphosphonate use, although small numbers limited firm conclusions.^{49,51,53} Despite the nonrandomized nature of the data, this study suggested that a short-term drug holiday of approximately 1 year may be safely performed in selected subjects.

Summary

Postmarketing reports have examined the association between several serious adverse events and long-term bisphosphonate use for the prevention and treatment of osteoporosis and raised concerns regarding the long-term safety of this class of antiresorptive medications. Because these adverse events seem to occur infrequently to date, conventional clinical trials are underpowered to provide conclusive evidence with regard to their long-term safety.

Several epidemiologic studies have been conducted using large databases from various sources and types. These studies consistently reported an association between intravenous bisphosphonate use for cancer treatment and ONJ. Although conflicting results have been reported regarding the association between bisphosphonate used for osteoporosis and atypical fractures, more recent studies suggested the risk of ONJ and atypical fractures may be increased among long-term users. In contrast to bone and jaw data, the association between bisphosphonate use and esophageal cancer has yielded largely inconsistent results to date.

Although these suspected adverse events can be severe, they occur infrequently. Given the efficacy of bisphosphonates in the reduction of vertebral and nonvertebral fractures, the benefits likely outweigh potential risk over the short term for most patients who require treatment for their osteoporosis. In contrast, the long-term use of these agents and, in particular, the selection of patients at higher risk and potentially with higher bone turnover, is an area of growing research interest and controversy. The case series and controlled epidemiologic studies covered in this review are helpful in alerting physicians to identifying patients perhaps who are at increased risk of developing these serious adverse events (eg, patients with Barrett's esophagus) or precursors to some of these events (ie, prodromal bone pain in the thigh). Because bisphosphonates continue to exert a protective effect a long time after treatment discontinuation and given the potentially elevated risk of developing these adverse outcomes suggested to occur in subjects taking long-term bisphosphonate, physicians may wish to evaluate the risk factors for these serious adverse events in patients who had received 5 years or more bisphosphonate treatment with regard to their fracture risk factors and consider a drug holiday in selected patients with their informed consent. In the future, with increased amount postmarketing surveillance data available, well-designed epidemiologic studies with access to clinical data (eg, x-ray images) will hopefully clarify the magnitude of these associations and whether they are real or spurious. Most importantly, future investigation is needed to provide more information on how to correctly identify those who are at most risk of developing these adverse events among bisphosphonate users and in identifying groups most appropriate to receive these drugs in the shorter term.

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