Drug-Related Adverse Events of Osteoporosis Therapy

Moin Khan, MD, MSc, FRCSC[a,1], Angela M. Cheung, MD, PhD, FRCPC[b,1], Aliya A. Khan, MD, FRCPC[a,*,1]

KEYWORDS

• Bisphosphonates • Denosumab • Raloxifene • Teriparatide
• Atypical femoral fractures • Osteonecrosis of the jaw

KEY POINTS

- Bisphosphonates and denosumab are effective in reducing the risk of vertebral, nonvertebral, and hip fracture and are well tolerated with only minor side effects with short-term use.
- Long-term use of bisphosphonates and denosumab is associated with a small increased risk of atypical femoral fracture and rarely osteonecrosis of the jaw; these uncommon adverse events can be prevented or identified early with close monitoring and patient education.
- Teriparatide, an anabolic agent, is effective in reducing the risk of vertebral and nonvertebral fracture and is well tolerated with minor side effects.
- Raloxifene and bazedoxifene are effective in lowering the risk of vertebral fracture only and are associated with hot flashes and an increased risk of thromboembolic events.
- Pharmacologic intervention requires careful review of fracture risk and in the absence of contraindications the benefits are far greater than the potential risk of therapy.

INTRODUCTION

Postmenopausal osteoporosis is associated with microarchitectural deterioration and an increased risk of fracture.[1] Osteoporosis therapy has been demonstrated to effectively reduce the risk of vertebral, nonvertebral, and hip fracture and also has been associated with increased survival.[1] Currently approved treatments for osteoporosis include bisphosphonates, denosumab, selective estrogen receptor modulators, and

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[a] McMaster University, 1200 Main Street West, Hamilton, ON L8N 3Z5, Canada; [b] University of Toronto, 200 Elizabeth Street, 7 Eaton North Room 221, Toronto, ON M5G 2C4, Canada
[1] Present address: #223, 3075 Hospital Gate, Oakville, Ontario, Canada.
* Corresponding author.
E-mail address: Aliya@mcmaster.ca

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teriparatide.[1] This article reviews the adverse events of therapy associated with these medical interventions. Hormone replacement therapy is not included, because it is no longer indicated as first line therapy for the treatment of osteoporosis in all countries. Calcitonin and strontium ranelate also are not included, because their indication for osteoporosis has recently been limited or withdrawn.

BISPHOSPHONATES

Amino-bisphosphonates (aBPs) have been demonstrated to be effective in reducing the risk of fragility fracture in postmenopausal osteoporosis, osteoporosis in men, and glucocorticoid-induced osteoporosis as noted in pivotal fracture trials.[1] Currently, alendronate, risedronate, ibandronate, and zoledronate are approved for the treatment of postmenopausal osteoporosis. These compounds are not metabolized by any organ system and have few systemic side effects. They are cleared through the kidney and are contraindicated in stages 4 and 5 chronic kidney disease (estimated glomerular filtration rate is <30–35 mL/min).

Dosing and Administration

Alendronate is administered orally 70 mg weekly or 10 mg daily. Risedronate is administered orally 5 mg daily or 35 mg weekly or 150 mg monthly. Zoledronate is administered intravenously 5 mg over 15 to 30 minutes annually.[1]

Side Effects

Gastroesophageal adverse events

Oral aBPs have been associated with gastrointestinal side effects, including nausea, epigastric pain, esophagitis, and gastric ulcer.[2] Oral aBPs may impair the healing of esophageal acid–induced injury and are contraindicated in the presence of gastroesophageal reflux.[3] These side effects may be more pronounced with the use of generic oral bisphosphonates.[4]

Acute phase response

Intravenous zoledronic acid administration may be associated with an acute phase response usually observed after the first infusion and occurs in approximately 30% of patients.[5] This response is characterized by myalgias, arthralgias, low-grade fever, headache, and bone pain.[5] It usually resolves in 3 to 4 days and is less common with subsequent infusions. The acute phase response appears to be mediated by the release of cytokines (interleukin-6 and tumor necrosis factor-a) by activated T cells, resulting in an inflammatory response.[6,7]

Atrial fibrillation

An association between atrial fibrillation and the use of bisphosphonates was suggested in the phase 3 trial for zoledronic acid in comparison with placebo[8] (1.3% vs 0.5%, $P<.001$).[8] An increased risk of atrial fibrillation was observed, as well, in a small case control study with alendronate use.[9] A subsequent meta-analysis confirmed no association between the use of bisphosphonates and the development of atrial fibrillation.[10,11]

Esophageal cancer

The possible association between oral bisphosphonate use and esophageal cancer has been evaluated in the UK General Practice Research Database Cohort and an increase in the risk of esophageal cancer from 1 case per 1000 to 2 cases per 1000 patients with 5 years of use was reported.[12] A reanalysis of the same data did not confirm

an association between oral bisphosphonate use and esophageal cancer risk.[13] Other investigators have also not identified an association between oral bisphosphonate use and the development of esophageal cancer in a Danish open cohort registry–based study.[14]

Uveitis, scleritis, and conjunctivitis

Ocular side effects can rarely occur with intravenous as well as oral aBP use and reports of uveitis, scleritis, and orbital inflammatory disease have been published.[15–17] A retrospective review suggests an incidence of 0.8% for the development of acute uveitis.[18] A recent prospective study evaluated the incidence of ocular side effects occurring within 3 months of receiving intravenous zoledronate 5 mg or placebo in 1054 postmenopausal women.[19] Fourteen individuals developed ocular symptoms following the infusion. The incidence of acute anterior uveitis and episcleritis was 1.1% (95% confidence interval [CI] 0.5–2.1) and 0.1% (95% CI 0.0–0.7), respectively, for the zoledronate group with no cases in the placebo group. The mean time for the development of symptoms was 3 days (range 2–4) Topical treatment with cyclopentolate and corticosteroids was initiated with no long-term sequelae. None of the individuals lost vision.[19] It is recommended to inform patients about the possibility of ocular side effects with intravenous zoledronate infusion.

Atypical femoral fractures

Incidence and risk factors Epidemiologic studies have confirmed an increased risk of femoral shaft and subtrochanteric fractures with prolonged use of bisphosphonates.[20–22] Randomized control trials of bisphosphonates in comparison with placebo have not demonstrated an increased risk of atypical femoral fractures (AFFs) and this may be a reflection of the relatively small number of individuals enrolled in the randomized control trials.[23–25] A systematic review and meta-analysis of published studies evaluating the association of bisphosphonates with subtrochanteric femoral shaft fractures and AFFs included 11 studies, 5 of which were case control and 6 were cohort studies.[26] Bisphosphonate exposure was associated with an increased risk of subtrochanteric femoral shaft fractures and AFFs with an adjusted relative risk of 1.70 (95% CI 1.22–2.37).[26] The risk of AFFs during and after bisphosphonate use was evaluated in Sweden in a nationwide cohort study.[27] Radiographs of 5342 Swedish women and men ages 55 and older who had experienced a femoral shaft fracture between 2008 and 2010 were reviewed, and 172 patients had AFFs.[27] The age-adjusted relative risk of atypical fracture with bisphosphonate use was 55 (95% CI 39–79) in women and 54 (CI 15–192) in men.[27] Women had a threefold higher risk of AFF in comparison with men. The risk of an AFF decreased by 70% per year following cessation of bisphosphonate use.[27]

AFFs appear to be more common in Asian women in comparison with white women.[28] A greater proportion of Asian women were noted to have AFFs in association with long-term bisphosphonate use in comparison with white women on long-term bisphosphonate therapy.[28] The risk of AFF increases with duration of bisphosphonate use and rises after 3 to 4 years with even greater increases in risk after 6 to 20 years of use.[27,29]

Other risk factors that have been identified for AFF include a slightly higher body mass index (26.2 ± 5.1 kg/m^2 vs 23.6 ± 6.2 kg/m^2).[30] Associations with oral glucocorticoid use, statins and proton pump inhibitor use have also been described.[30,31] Prodromal symptoms have been reported in 51.6% of patients.[30] Other investigators have found prodromal symptoms with thigh pain in 69% of patients.[29]

Pathophysiology The pathophysiology resulting in AFF is not clearly understood. Prolonged suppression of bone remodeling may result in accumulation of microcracks that may not be repaired.[32] Bisphosphonate therapy increases bone mineralization and may result in a uniform or homogeneous pattern of mineralization enabling crack propagation and may increase the risk of stress fracrtures.[33] Bone biopsy data are currently not conclusive and the underlying pathophysiology leading to AFF remains unclear.

The proximal femur geometry may also impact the likelihood of developing an AFF.[30] The presence of proximal femoral varus and a narrow femoral neck width was seen more frequently in individuals with AFF in comparison with controls.[30] Thicker lateral and medial bone cortices were also seen more frequently in patients with AFF in comparison with controls.[30] There may be a correlation between the lateral bowing angle of the femur and the location of the AFF.[34] These geometric risk factors also need to be further evaluated in large prospective studies.[35]

Osteonecrosis of the jaw

Definition Osteonecrosis of the jaw (ONJ) was first described in association with bisphosphonate use in oncology patients.[36] The definition of ONJ was clarified by the American Society for Bone and Mineral Research.[37] ONJ is defined as an area of exposed bone in the maxillofacial region that does not heal within 8 weeks in an individual who has been exposed to an antiresorptive agent and has not had radiation therapy.[37] Other risk factors for ONJ include chemotherapy, major oral surgery, periodontal disease, antiangiogenic drugs, diabetes, and glucocorticoid therapy. ONJ has significant morbidity and requires careful follow-up by an oral surgeon.[38]

ONJ lesions can remain asymptomatic for weeks or several months. They subsequently become symptomatic with inflammation in the surrounding tissues and can present with pain, swelling, ulceration, paresthesias, and tooth mobility.[39–41]

Incidence The incidence of ONJ is estimated largely from case series, retrospective observational data, and retrospective cohort data, because very limited prospective data evaluating the true incidence of ONJ in patients with osteoporosis are currently available. The incidence of ONJ in patients with osteoporosis is approximately 0.01% to 0.001%.[42–53]

Postmarketing of alendronate, Merck (New Jersey) estimated the incidence of ONJ to be less than 1 in 100,000 following exposure to alendronate. In the HORIZON study with 7765 postmenopausal women randomized to zoledronic acid in comparison with placebo, there were 2 cases of ONJ identified.[49] One was in a patient with a dental abscess and receiving zoledronic acid, the other occurred in a patient receiving placebo and prednisone therapy. Both of these cases resolved with antibiotics and debridement. Four additional clinical trials with zoledronic acid were reviewed and no additional cases of ONJ were identified. The incidence of adjudicated ONJ in 5903 patients treated with zoledronic acid in the 5 clinical trials was less than 1 in 14,200 patient treatment-years.[49]

In the oncology patient population receiving high doses of intravenous aBPs, the incidence of ONJ is higher and is estimated to be approximately 1% to 15%. The quality of evidence in the oncology patient population is much greater with both prospective and retrospective published studies. The oncology patient population is exposed to other risk factors associated with ONJ, including glucocorticoid therapy, chemotherapy, antiangiogenic agents, and radiotherapy. High-dose aBP therapy is associated with greater osteoclast inhibition. In patients with cancer, the incidence of ONJ appears to be related to the dose and duration of bisphosphonate therapy.[54–57]

The first large prospective evaluation of ONJ was in 5723 oncology patients with metastatic bone disease. These individuals were enrolled in 3 registration trials comparing denosumab 120 mg with zoledronic acid 4 mg given monthly. Oral examinations were conducted every 6 months, and 89 adjudicated cases of ONJ were identified. The incidence of ONJ with zoledronic acid and denosumab was not statistically different in this 36-month study.[54] The ONJ resolution rate appeared to be greater in individuals receiving denosumab in comparison with zoledronic acid; however, this requires further evaluation. Skeletal-related events were significantly decreased and the benefit of therapy greatly outweighed the risk of ONJ by a factor of 17.[54] In the oncology patients being prospectively evaluated, most individuals with ONJ developed ONJ in association with an oral event, such as a tooth extraction, in two-thirds of patients. Coinciding oral infection was seen in one-half of the patients and patients also had other risk factors for ONJ, such as the use of glucocorticoid therapy, which was seen in 73% of patients with ONJ in comparison with 62.3% without ONJ. Antiangiogenic agents were used in 15.7% of patients with ONJ and only 8% without ONJ.[54]

In the oncology patient population, risk factors for ONJ include intravenous bisphosphonate use, denosumab exposure, dental extractions, chemotherapy, periodontal disease, glucocorticoid therapy, diabetes, denture use, smoking, hyperthyroidism, dialysis, antiangiogenic agents, and being of older age.[57–67]

Pathophysiology Decreases in bone remodeling and osteocyte death appear to be factors in the development of ONJ. Infection also plays a key role in the development of ONJ and can contribute to and result from destruction of the oral mucosa. Infection may precede or follow necrosis and bacteria and polymorphonuclear leukocytes are usually seen in ONJ tissue.[68,69] Bacteria stimulate bone resorption and may contribute to the development bone necrosis.

Bisphosphonates can impact the immune response by having an impact on gamma-delta T cells and lead to macrophage dysfunction.

Bisphosphonates can activate the gamma-delta T cells and impact the immune response to infeca T cells and impact the immune response to infection.[70–72] Suppression of bone remodeling appears to play a role in the development of ONJ.[73,74]

Bisphosphonates have been demonstrated to have antiangiogenic effects[71,75] and may contribute to the development of ONJ. Antiangiogenic agents also may play a key role in the development of ONJ.

Prevention of osteonecrosis of the jaw The risk of ONJ appears to decrease with conservative therapy, including antimicrobial mouth rinses[38] and antibiotics before and after oral surgery.[38] Maintaining good oral hygiene is of key importance in preventing the development of ONJ.[38] It is recommended that oral surgery be completed before initiation of high-dose antiresorptive therapy in oncology patients. In this population, dental radiographs also should be obtained before initiation of high-dose antiresorptive therapy with identification of dental disease before initiation of antiresorptive therapy.[38] Any necessary dental procedures, including dental extraction or implants should be completed before initiation of therapy. Nonurgent procedures may be delayed if necessary. If they are urgently required, then they can be performed and the oncology doses of bisphosphonate or denosumab may be withheld until soft tissue closure is achieved. Currently, there is no evidence that interrupting drug therapy for patients requiring dental surgery will reduce the risk of ONJ or the progression of the disease. Delaying antiresorptive therapy until the surgical site heals in individuals at a high risk of ONJ may be of value of reducing the probability of ONJ.[38] In determining the suitability of

drug interruption, the risk of ONJ must be weighed with the risk of skeletal-related events in oncology patients as well as the risk of fracture in individuals with osteoporosis.[38] In individuals with osteoporosis receiving low doses of bisphosphonate or denosumab therapy, antiresorptive treatment may be continued in the absence of significant comorbidity. The management decisions regarding interruption of drug therapy are ideally made by the dental and medical team managing patient care.

DENOSUMAB

Denosumab, an inhibitor of RANKL (receptor activator of nuclear factor KB), is a potent antiresorptive agent and is generally well tolerated. It is effective in lowering the risk of vertebral, hip, and nonvertebral fracture in postmenopausal osteoporosis.[76]

Dosing and Administration

Denosumab is administered subcutaneously in doses of 60 mg every 6 months.

Side Effects

In comparison with placebo, serious side effects were observed in 24.9% of individuals in comparison with 23.8% of controls.[77] In the FREEDOM study, there were no significant differences reported for side effects evaluated separately.[76] Arthralgias have been reported more frequently with denosumab in comparison with placebo (16.6% vs 14.3%); however, this difference has not been a statistically significant difference.[77] Symptomatic hypocalcemia occurred in 0.01% of individuals in the denosumab group in comparison with 0.05% of individuals in the placebo group. As denosumab is a potent antiresorptive agent, it is essential to ensure that serum calcium is normal before starting denosumab and also to ensure that patients are vitamin D replete, as vitamin D insufficiency can contribute to the development of hypocalcemia with denosumab therapy.

Dermatitis can be seen as an uncommon side effect.

Following introduction of denosumab in the market, several case reports have been published of AFF in individuals treated with denosumab.[78] In the FREEDOM study evaluating denosumab in comparison with placebo, 2 AFFs have been observed. One was in the cross-over arm, with 6 doses of denosumab use and one occurred in the long-term arm with 14 doses of exposure (Amgen, personal communication, 2015). The number needed to harm for denosumab has been estimated to be 1 in 10,000.

In the population of patients with osteoporosis receiving denosumab therapy, ONJ cases have been identified. The incidence appears to be very low and appears to be only slightly greater than that seen in the general population.

In the FREEDOM clinical trial of denosumab versus placebo involving almost 8000 postmenopausal osteoporotic women over 3 years, there were no cases of ONJ. In the extension of the FREEDOM study to 7 to 10 years of exposure, 13 cases of ONJ were identified.[79]

The postmarketing exposure to denosumab has been estimated to be 1,960,405 patient-years in 2,427,475 patients as of May 2014.[80] Following this exposure, 47 cases of adjudicated ONJ (based on the American Association of Oral and Maxillofacial Surgeons criteria) have been confirmed. All of these individuals had at least one other risk factor for ONJ. These included concurrent glucocorticoid use, concurrent chemotherapy, prior bisphosphonate use, or invasive dental procedures. The ONJ lesions resolved in a third of the cases and are ongoing in another third. The status of the remaining one-third is not known.[80]

TERIPARATIDE

Teriparatide is the only anabolic agent currently approved for the treatment of postmenopausal osteoporosis. It has been demonstrated to effectively reduce the risk of vertebral and nonvertebral fracture.[81] The pivotal fracture trial was terminated early and only 5 hip fractures were observed in the study. There were 4 hip fractures in the placebo group and 1 in the teriparatide group and the CI crossed 1.[1]

Dosing and Administration

Teriparatide is administrated subcutaneously in doses of 20 μg daily for up to 2 years.

Side Effects

This drug is also well tolerated. Adverse events observed in patients include nausea, headache, dizziness, and leg cramps.[81]

In carcinogenicity studies with rats, near lifetime treatment with systemic exposure ranging from 3 to 60 times the exposure in humans was associated with osteosarcoma in rats.[82] Osteosarcoma, however, has not been observed in humans, and the incidence of osteosarcoma in individuals treated with teriparatide is no different from the incidence seen in the general population. In the US postmarketing surveillance study of adult osteosarcoma and teriparatide, there was no association between teriparatide treatment and osteosarcoma in humans.[83]

SELECTIVE ESTROGEN RECEPTOR MODULATORS

Raloxifene and bazedoxifene have been demonstrated to reduce the risk of vertebral fracture in comparison with placebo.[1] A reduction in the risk of nonvertebral or hip fracture risk has not been observed in studies completed to date.

Dosing and Administration

Raloxifene is administered orally 60 mg daily.

Side Effects

Raloxifene has been evaluated in comparison with placebo,[84] as well as in comparison with tamoxifen in a head-to-head trial.[85] The drug is well tolerated with side effects limited to hot flashes, vaginal dryness, and a small increase in the risk of thromboembolic events.[84] In comparison with tamoxifen, raloxifene had a better safety profile, with 36% fewer uterine cancers and 29% fewer deep vein thromboses.[85]

In the RUTH study conducted in 10,101 postmenopausal women assigned to raloxifene 60 mg daily versus placebo for a median of 5.6 years, raloxifene was associated with a 50% decrease in the risk of invasive breast cancer.[86] The risk of vertebral fractures decreased by 35%.[86] There was a 50% increase in the risk of venous thromboembolic events and an increase in the risk of fatal stroke by 49%.[86]

SUMMARY/FUTURE CONSIDERATIONS

Osteoporosis therapy is safe and generally well tolerated. The benefits of therapy greatly outweigh potential harm. Selecting the best drug for each patient requires a review of the fracture risk for each patient as well as their suitability for the drug with respect to potential adverse effects. The risk for long-term adverse effects can be minimized by close follow-up of patients and advising patients to report the development of prodromal symptoms of an AFF. Interruption of bisphosphonate therapy after 3 to 5 years is also of value in reducing the potential risk of AFF.

Sequential use of anabolic therapy following prolonged antiresorptive therapy appears to be a valuable strategy in reducing both fracture risk and the risk of long-term adverse events in association with prolonged suppression of bone remodeling. The risk of ONJ also can be minimized by advising patients to ensure good oral hygiene is maintained in addition to regular dental care. Patient education is key to minimizing the actual and perceived adverse events of therapy while ensuring compliance with the available treatment options today.

Future directions for research include development of new anabolic molecules and the development of sequential therapy strategies designed to lower the risk of fracture while minimizing the potential risks of oversuppression of bone remodeling. Advances in imaging will also be of value in the early detection of AFF and ONJ. Identification of individuals with genetic predisposition for the development of AFF or ONJ will also be of value in selecting the best treatment option for each individual patient.

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