Drug-Related Adverse Events of Osteoporosis Therapy

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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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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and strontium ranelate also are not included, because their indication for osteoporosis has recently been limited or withdrawn.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