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Bisphosphonates for Postmenopausal Osteoporosis

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Bisphosphonates are the first-line pharmacologic treatment for postmenopausal osteoporosis and the most commonly prescribed medication for this condition.[1] Bisphosphonates, classified as antiresorptive agents, have a very high affinity for bone mineral and bind to hydroxyapatite crystals on bony surfaces, where they inhibit osteoclast-mediated bone resorption.

Clinical Use

The primary goal of osteoporosis drug treatment is to reduce risk of clinical fractures. Guidelines agree that pharmacologic therapy should be initiated in postmenopausal women with osteoporosis manifested by a hip or spine bone mineral density (BMD) T score less than or equal to −2.5 or personal history of fragility fracture (eg, hip, radiographic or clinical vertebral). Some organizations also recommend treatment initiation in postmenopausal women with osteopenia (BMD T score between −2.5 and −1.0) who have a 10-year fracture probability (calculated using the FRAX tool) at or above intervention thresholds proposed by the National Osteoporosis Foundation, but the benefit of treatment in patients selected on the basis of these criteria has not been assessed in clinical trials.

Supplemental content

A suggested approach for initiating bisphosphonates to manage postmenopausal osteoporosis is shown in the **Figure**. Treatment with alendronate, risedronate, or zoledronate lowers risk of vertebral and nonvertebral fractures, including hip fractures (eTable in the Supplement). Network meta-analyses suggest that differences in effectiveness between these 3 bisphosphonates are likely to be small.[2] In contrast, there is no evidence that ibandronate reduces risk of nonvertebral fractures (eTable in the Supplement). Thus, alendronate or risedronate is the treatment of choice for most patients initiating oral bisphosphonates. Contraindications to the use of oral bisphosphonates include achalasia, esophageal stricture, and Barrett esophagus, but oral bisphosphonates are often well-tolerated in patients with a distant history of peptic ulcer disease or with gastroesophageal reflux managed with medications.[1] Patients with gastrointestinal (GI) contraindications to or GI adverse effects with oral bisphosphonates and those who are or likely to have poor adherence to oral bisphosphonates are candidates for intravenous (IV) zoledronate. Because bisphosphonates may accumulate in patients with impaired kidney function, oral or IV bisphosphonates are not recommended in patients with a creatinine clearance less than 30 to 35 mL/min. Correction of hypocalcemia and vitamin D deficiency is necessary prior to bisphosphonate administration. All bisphosphonates are available in generic form.

Potential Harms of Bisphosphonate Treatment

Osteonecrosis of the jaw (ONJ) and atypical femoral fractures (AFFs) are rare but serious potential harms of treatment with bisphosphonates. While the frequency of ONJ (exposed bone in the maxillofacial region that does not heal within 8 weeks) in patients receiving high-dose IV bisphosphonate (eg, zoledronate) for management of hypercalcemia of malignancy is 1% to 15%, the incidence of ONJ in patients with osteoporosis receiving oral or IV bisphosphonate is substantially smaller, between 1 in 10 000 and 1 in 100 000 per year of use.[3] AFFs (low-trauma subtrochanteric or femoral shaft fractures with unusual radiologic features including a transverse morphology and thickened cortices) typically occur with little or no antecedent trauma, may be preceded by groin pain, and may occur bilaterally. AFFs require surgical management and may be complicated by delayed healing. Although bisphosphonate use is associated with a 1.7-fold increase in risk of AFFs,[4] the absolute risk of AFFs among bisphosphonate users treated for 5 years or less is very low. It is estimated that for every 10 000 women treated with bisphosphonates for 3 years, 130 hip fractures will be prevented at the cost of 1 AFF.[5] However, incidence of AFFs increases with longer duration of bisphosphonate treatment. Age-adjusted incidence rates rise from 1.8 per 100 000 persons per year with a 2-year exposure up to 113 per 100 000 persons per year with an 8- to 10-year exposure.[6] Thus, while the benefits of bisphosphonate treatment outweigh the risk of AFFs early in treatment, this balance is less clear for long-term users.

Duration of Bisphosphonate Treatment

There is uncertainty about the ideal duration of bisphosphonate treatment. Bisphosphonates have a long half-life in bone. Thus, stopping bisphosphonates does not result in cessation of action. Two randomized trials evaluating the benefits of continuing vs discontinuing bisphosphonate treatment showed that in treatment-naive women who received zoledronate for 3 years or alendronate for 5 years, continuation inconsistently reduced vertebral fracture outcomes and did not reduce nonvertebral fractures.[7] These limited data suggest that fracture risk reduction may persist years after discontinuation of bisphosphonate treatment.

A recent American College of Physicians guideline recommended that clinicians treat postmenopausal women with osteoporosis with bisphosphonates for 5 years,[8] but suggested that high-risk patients may benefit from longer treatment. Other organizations[9] recommend the institution of a drug holiday (eg, temporary discontinuation of bisphosphonate followed by reassessment in 2-3 years) in select patients, such as those without a fragility fracture before or during therapy who have a hip BMD T score greater than −2.5 after the initial treatment period. However, evidence is insufficient to make recommendations about the exact timing and duration of bisphosphonate drug holidays.

Alternative Antiresorptive Medications

Denosumab, a biologic therapy, is an alternative initial treatment. It is the therapy of choice for patients with contraindications or intolerance to bisphosphonates. Denosumab reduces risk of vertebral and nonvertebral fractures, including hip fractures (eTable in the Supplement). Hypocalcemia and vitamin D deficiency must be corrected prior to initiation of denosumab. Similar to the bisphosphonates, rare (but serious) harms of denosumab include ONJ and AFFs. Unlike the bisphosphonates, treatment with denosumab results in BMD gains that rapidly wane after discontinuation of treatment. Among patients who discontinue denosumab, higher rates of vertebral

Figure. Suggested Starting Regimen for Oral Bisphosphonates, Common Obstacles to Use, and Alternative Antiresorptive Medications

First-line oral bisphosphonate treatment for postmenopausal osteoporosis

Recommended initial treatment	Optional initial treatment
Alendronate (70 mg/wk) or risedronate (35 mg/wk or 150 mg/mo)	Consider intravenous (IV) zoledronate (5 mg every 12 mo) to eliminate risk of gastrointestinal (GI) adverse effects and ensure adherence

Common obstacles to using oral bisphosphonates

Condition or obstacle	Recommended approach
GI intolerance to oral bisphosphonates	Emphasize adherence to dosing instructions and consider use of IV zoledronate
Impaired kidney function	Do not use oral or IV bisphosphonates if creatinine clearance is less than 30-35 mL/min
Poor adherence to treatment	Consider use of IV zoledronate
Concerns about serious harm caused by oral bisphosphonates	Consider oral health prior to bisphosphonate initiation; consider limiting initial treatment period to no more than 5 years; and reassess whether to reinitiate treatment 2-3 years after discontinuation

Alternative antiresorptive medications

Medication	Pros	Cons	Potential risks
Denosumab (subcutaneous, 60 mg every 6 mo)	• Reduces vertebral and nonvertebral fractures (including hip fractures) • Can use if creatinine clearance is less than 30-35 mL/min	• High cost • Requires injections every 6 months	• Osteonecrosis of the jaw, atypical femoral fractures, rebound vertebral fractures upon discontinuation, and hypocalcemia
Raloxifene (oral, 60 mg daily)	• Reduces vertebral fractures • Reduces breast cancer in high-risk women	• No reduction in nonvertebral or hip fractures	• Venous thromboembolic events

fractures have been reported.[10] Thus, patients treated with denosumab should either continue treatment indefinitely or transition to an alternative antiresorptive medication upon discontinuation. Whether risk of AFF increases with increasing duration of denosumab treatment is uncertain. Clinicians considering denosumab treatment must acknowledge uncertainties about benefits vs risks of long-term treatment and counsel patients not to abruptly discontinue treatment.

Raloxifene, a selective estrogen receptor modulator, reduces risk of vertebral fracture (but not nonvertebral fracture) (eTable in the Supplement). Thus, raloxifene is not a first-line treatment. Long-term use of raloxifene decreases risk of breast cancer among women at higher risk for this condition, but also increases the risk of venous thromboembolic events.

Estrogen plus progestin or estrogen alone are not approved by the US Food and Drug Administration for management of postmenopausal osteoporosis. Fracture prevention benefits do not outweigh the harms of these antiresorptive agents for most patients.[7]

Conclusions

Due to their efficacy in fracture prevention, availability of long-term safety data, and cost advantage over several other agents, bisphosphonates remain the first-line pharmacologic treatment for postmenopausal osteoporosis. Concerns about potential harms may be mitigated by targeting treatment to patients with higher absolute fracture risk, such as older women, women with previous fracture, and women with BMD T scores less than or equal to −2.5; having good communication with patients; and limiting the treatment period to 5 years or less in patients without a fragility fracture before or during therapy who achieve a BMD T score greater than −2.5 while receiving treatment.

ARTICLE INFORMATION

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