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**Review Article**

# A Clinician's Perspective on the Use of Zoledronic Acid in the Treatment of Postmenopausal Osteoporosis

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## Abstract

Osteoporotic fractures may lead to pain, disability, impaired quality of life, and increased risk of death, with annual health-care costs of $17 billion or more. Oral bisphosphonates, the first-line treatment for postmenopausal osteoporosis (PMO), increase bone mineral density and reduce the risk of fracture, but dosing requirements are complex and compliance and persistence are poor. The newest bisphosphonate treatment option, intravenous (IV) zoledronic acid (ZOL) every 12 mo, has been shown to reduce the risk of vertebral, hip, and other nonvertebral fractures. Long-dosing intervals and 100% bioavailability with IV bisphosphonate therapy address some of the limitations associated with oral bisphosphonates. This is a review of the clinical trial data supporting the use of IV ZOL to reduce fracture risk, and its potential role in the management of PMO in clinical practice.

**Key Words:** Bisphosphonates; osteoporosis; treatment; zoledronate; zoledronic acid.

## Introduction

Dual-energy X-ray absorptiometry (DXA) is the gold-standard technology for measuring bone mineral density (BMD) for the purpose of diagnosing osteoporosis, assessing fracture risk, and monitoring changes in BMD over time. The World Health Organization has defined osteoporosis as a BMD of at least 2.5 standard deviations (SDs) below the mean BMD of a young adult reference population (T-score −2.5 or less) as determined by a DXA of the spine, hip, or forearm *(1)*. There is a 1.5- to 2.6-fold increase in relative fracture risk for every SD decrease in BMD *(2)*. The International Society for Clinical Densitometry and the National Osteoporosis Foundation (NOF) indications for BMD testing include all women aged 65 yr and older, all men aged 70 yr and older, younger postmenopausal women and men aged 50−70 yr with risk factors for osteoporosis, and women in the menopausal transition with risk factors *(3,4)*.

The combination of BMD and clinical risk factors for fractures predicts fracture risk better than BMD alone. The most important of these risk factors are increasing age and prior fragility fracture. Fracture risk increases with advancing age, regardless of baseline T-score; for example, a T-score of −2.5 represents a 6% 10-yr fracture probability in a 50-yr-old woman, but a 26.5% 10-yr fracture probability in an 80-yr-old woman *(5)*. A prevalent vertebral fracture increases the risk of another fracture by about 5-fold in the year following the primary fracture *(6,7)*.

Once a decision to treat is made, a specific drug must be selected. Bisphosphonates are the accepted first-line therapy for most patients with postmenopausal osteoporosis (PMO). Drugs in this class increase bone strength and reduce fracture risk by inhibiting osteoclast activity and inducing osteoclast apoptosis, thereby reducing bone resorption and increasing BMD *(8)*. Oral formulations are available for administration daily (alendronate, risedronate), weekly (alendronate, risedronate), and monthly (ibandronate, risedronate). Oral bisphosphonates are poorly absorbed (less than 1%) and may be associated with esophageal irritation/gastrointestinal symptoms when used in clinical practice. They must be taken with plain water on an

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empty stomach after an overnight fast, with a postdose fast and upright position for 30 min (alendronate, risedronate) or 60 min (ibandronate). Two intravenous (IV) bisphosphonates are approved by the US Food and Drug Administration (FDA) for the treatment of PMO: ibandronate and zoledronic acid (ZOL). This review will focus on unmet needs in the management of osteoporosis and the potential clinical applications of the most recently approved bisphosphonate for treating PMO, ZOL 5 mg IV every 12 mo.

## Barriers to Effective Management of Osteoporosis

### *Underdiagnosis and Undertreatment*

The US Surgeon General has identified osteoporosis as a disease that is underdiagnosed and undertreated *(9)*. Gehlbach et al showed that 50% or fewer of women at risk for fracture in the United States are being treated with antiresorptive agents to reduce fracture risk, and only 17% of those at the highest level of risk are being treated *(10)*. In the hospital setting, recognition of osteoporosis has improved over the past decade, but is still suboptimal *(11)*. In a 2006 study of osteoporosis management in the hospital, only 41% of women with radiographic vertebral fracture had their fracture noted in the findings section of the X-ray report *(12)*.

### *Suboptimal Adherence to Prescribed Treatment Regimens*

Compliance and persistence (often collectively called adherence) to therapy for osteoporosis is poor *(13)*, as it is for many other medical disorders *(14)*, including acute symptomatic diseases *(15)* and life-threatening diseases *(16)*. In a longitudinal cohort study, only about 33% of patients on daily regimens and 45% on weekly regimens for osteoporosis achieved adequate adherence, defined as having taken more than 80% of their prescribed medication *(17)*. Many patients—about 68% of those on daily regimens and 56% of those on weekly regimens—had discontinued treatment by 12 mo from initiation. Other studies have shown similar trends *(18)*. In a study of a large, geographically diverse managed care plan, adherence to therapy among patients treated with alendronate (n = 6881) or risedronate (n = 2224) was evaluated. Persistence, defined as continuous therapy on the same drug for each month over the study period, was comparable between weekly and daily users; both exhibited drop-off within the first 3 mo, followed by a steady decline through month 12 *(19)*.

### *Consequences of Suboptimal Adherence to Therapy*

Poor adherence to osteoporosis therapy is associated with higher medical costs *(20)* and poorer clinical outcomes, including greater risk of fractures, compared with good adherence to therapy. An analysis of data from 2 US claims databases with 35,537 women aged 45 yr and older who received a bisphosphonate prescription calculated the probability of a fracture as a function of medication possession ratio (MPR; the number of days the patient was in possession of the drug divided by the number of days of follow-up) *(21)*. It was found that there was no protection against fracture if patients took less than 50% of their medication (MPR $<$ 50%); risk was reduced modestly if they took 50−74% (MPR of 50−74%); and it was reduced sharply if they took $\geq$75% of their medication (MPR $\geq$ 75%). It is imperative for health-care providers to use effective strategies to optimize adherence to therapy to achieve the full benefit of effective medical therapy *(22)*.

## Overcoming Treatment Barriers

### *Improving Adherence to Therapy*

The US Surgeon General has identified poor adherence to therapy as a major obstacle in relieving the burden of osteoporotic fractures, and recommended that research be conducted to determine the most effective doses, dosing schedules, and methods of administration to prevent fractures *(9)*. He queried whether lower doses, shorter courses, or wider spacing of treatment might help. Although oral bisphosphonates are effective and safe medications for the reduction of fracture risk, their clinical utility is limited by poor adherence to therapy that is in part due to the frequency of dosing, inconvenience of administration, and gastrointestinal (GI) side effects *(18,23)*. Weekly and monthly oral dosing are generally preferred by patients over daily dosing, and are associated with improved but still suboptimal adherence to therapy *(24−26)*. Bisphosphonates administered intravenously avoid concerns regarding incorrect oral administration (e.g., drinking with liquids other than plain water, insufficient postdose fasting), GI intolerance, and malabsorption. Whether IV bisphosphonates are associated with improved long-term adherence to therapy or greater reduction in fracture risk than oral bisphosphonates is not known. There have been no head-to-head clinical trials comparing the efficacy of different bisphosphonates with fractures as the primary endpoint. Extended dosing intervals with IV bisphosphonates (every 12 mo with ZOL or every 3 mo with ibandronate) certainly provide a longer period of antiresorptive effect than daily, weekly, or monthly oral dosing.

### *IV Bisphosphonates*

IV ibandronate (Boniva® in the USA, Bonviva® in other countries; Roche Pharmaceuticals, Inc., Nutley, NJ) was the first injectable bisphosphonate approved for the treatment of PMO. It is administered with a prepackaged syringe in a dose of 3 mg over 15−30 s every 3 mo. IV ibandronate is approved for the treatment of PMO based on a clinical trial *(27)* that demonstrated BMD increases and reduction in bone turnover markers at least as great as with daily 2.5 mg oral dosing, a regimen that has been proven to reduce fracture risk *(28)*. Pamidronate (generic; Aredia®, Novartis Pharmaceutical Corporation, East Hanover, NJ) is an IV bisphosphonate approved for use in patients with hypercalcemia of malignancy, osteolytic bone metastases of breast cancer and osteolytic lesions of multiple myeloma, and Paget's disease