THE AMERICAN JOURNAL of MEDICINE®

Efficacy of Bisphosphonates in Reducing Fracture Risk in Postmenopausal Osteoporosis

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ABSTRACT

Bisphosphonates have been available for more than a decade. Currently, 4 bisphosphonates—alendronate, risedronate, ibandronate, and zoledronic acid—are approved in the United States. Alendronate and risedronate are oral agents, ibandronate is available in oral and intravenous formulations, and zoledronic acid is an intravenous drug. This review summarizes results from pivotal clinical trials in which these bisphosphonates have been shown to reduce risk for osteoporotic fractures. Also reviewed are results of "bridging" studies designed to demonstrate the comparable efficacy of less frequent dosing regimens to increase bone mineral density and to reduce bone turnover. Compared with placebo controls, all 4 approved bisphosphonates reduce the relative risk of new vertebral fractures in women with postmenopausal osteoporosis. Alendronate, risedronate, and zoledronic acid reduce the relative risk of new nonvertebral and hip fractures. Clinical trial extensions of up to 10 years with alendronate and 7 years with risedronate have shown that efficacy is maintained during long-term treatment.
 • *The American Journal of Medicine (2009) 122, S14–S21*

KEYWORDS: Osteoporosis; Bisphosphonates; Fracture; Postmenopausal osteoporosis; Bone mineral density; Clinical trials

Osteoporosis, the most common metabolic bone disease, is a major health problem, resulting in >2 million fractures in the United States each year. Approximately 50% of women >50 years of age will have an osteoporotic fracture in their lifetime.[1] Osteoporosis-related fractures are associated with significant morbidity and mortality, frequently resulting in chronic pain, disability, and death.[2] Attendant direct and indirect medical costs were estimated in 2005 to be $19 billion in the United States alone.[1] The incidence of osteoporosis and related costs are projected to double or triple in coming years as the population ages.[3-5] As a result, early diagnosis and effective long-term treatment will be critical not only from a clinical perspective but also for containment of skyrocketing healthcare costs.

Because bone mineral density (BMD) correlates positively with bone strength and helps to predict future fracture risk, dual-energy x-ray absorptiometry (DXA) to assess BMD at the hip and spine is central to the diagnosis of osteoporosis. The World Health Organization (WHO) defines osteoporosis as a hip or spine BMD of ≤2.5 SD below normal mean reference values for a young population that has reached peak bone mass.[6] The WHO has recently introduced a Fracture Risk Assessment Tool (FRAX; WHO Collaborating Center for Metabolic Bone Diseases, University of Sheffield, Sheffield, United Kingdom) to help predict the 10-year probability of a hip or other major osteoporotic fracture in untreated men and women between the ages of 40 and 90 years using femoral neck BMD and risk factors that are largely independent of BMD.[7] The non–BMD-associated risk factors are age, sex, prior fracture history, parental history of a hip fracture, smoking status, long-term use of glucocorticoids, rheumatoid arthritis, and excessive alcohol consumption. If the BMD value is not available and the patient's body mass index (BMI) is <21, the BMI value can be used as a surrogate marker. The FRAX tool is currently available free of charge,[8] and by 2009 it is expected that it will be incorporated into the software of many DXA machines across the United States.

Current National Osteoporosis Foundation (NOF) guidelines[5] state that treatment with pharmacologic agents should be considered in postmenopausal women and in men aged ≥50 years who present with any of the following: hip or

Statement of author disclosure: Please see the Author Disclosures section at the end of this article.

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0002-9343/$ -see front matter
doi:10.1016/j.amjmed.2008.12.003

vertebral fracture; T-score ≤ -2.5 at the femoral neck, total hip, or spine after appropriate evaluation to exclude secondary causes; or low bone mass and a 10-year probability of hip fracture $\geq$3% or a 10-year probability of major osteoporosis-related fracture $\geq$20% based on the FRAX calculation.

The major treatment goal for patients with osteoporosis is to prevent fractures by maintaining or increasing BMD and reducing excessive bone turnover. Bisphosphonates, a mainstay among the various classes of antiosteoporotic drugs, have been shown to increase BMD and to reduce the risk for osteoporotic fractures in numerous clinical trials.[9] In the United States, 4 bisphosphonates have been approved by the Food and Drug Administration (FDA) for the treatment and/or prevention of osteoporosis. Oral alendronate (Fosamax; Merck & Co., Inc., Whitehouse Station, NJ) and oral risedronate (Actonel; Procter & Gamble Pharmaceuticals, Inc., Cincinnati, OH) were approved in 1995 and 2000, respectively. In 2003, oral ibandronate (Boniva; Roche Therapeutics Inc., Nutley, NJ) was approved, followed by intravenous ibandronate in 2006. Most recently, intravenous zoledronic acid (Reclast; Novartis Pharmaceuticals Corporation, East Hanover, NJ) was approved in 2007.

This review summarizes the efficacy results from key pivotal clinical trials of alendronate, risedronate, ibandronate, and zoledronic acid for the treatment of osteoporosis.

ALENDRONATE

The Fracture Intervention Trial

In the Fracture Intervention Trial (FIT), postmenopausal women (54 to 81 years of age) with low femoral neck BMD were enrolled in 2 randomized, double-blind, placebo-controlled, multicenter studies. The first FIT study, FIT-1,[10] lasted 3 years and included 2,027 women (mean age, 71 years) who had $\geq$1 vertebral fracture at baseline, and the primary end point was new vertebral fractures. The second study, FIT-2,[11] lasted 4 years and included 4,432 women (mean age, 68 years) who had low bone density (BMD $\leq$0.68 g/cm^2) but no vertebral fractures at baseline, and the primary outcome was new clinical fractures. In both trials, all patients received concomitant calcium and vitamin D. The active-treatment groups received alendronate 5 mg/day for 2 years and alendronate 10 mg/day for the remainder of the trial.

After 3 years of treatment, among subjects with $\geq$1 vertebral fracture at study entry (FIT-1), 8% of those in the alendronate group and 15% of those in the placebo group had experienced a new morphometric vertebral fracture, a reduction of 47% ($P < 0.001$) (Figure 1A).[10] Significantly fewer subjects in the alendronate group than in the placebo group had hip fractures (2% vs. 1%; risk reduction, 51%; $P = 0.047$).

Among subjects without an initial vertebral fracture at baseline (FIT-2), a lower-risk population, new morphometric vertebral fractures had occurred in 4% in the placebo group and 2% in the alendronate group after a mean of 4.2 years of follow-up, a reduction of 44% ($P = 0.002$) (Figure 1B).[11] Hip fractures were not significantly reduced by alendronate compared with placebo (1% incidence for both groups; $P = 0.44$).

In both FIT trials, BMD measurements were significantly greater ($P < 0.001$) for alendronate than for placebo at the femoral neck, hip, and spine.[10,11]

The FIT Long-term Extension. A continuation of the FIT trials, known as the Fracture Intervention Trial Long-term Extension (FLEX),[12] was a double-blind, placebo-controlled trial designed to study the effects of continuation or discontinuation of alendronate treatment for an additional 5 years. A total of 1,099 women from the FIT studies, who had received a mean of 5 years of prior alendronate treatment, were rerandomized to alendronate 10 mg/day (30%), alendronate 5 mg/day (30%), or placebo (40%). At the beginning of the extension trials, the average subject age was 73 years, with lumbar spine and total hip BMD mean T-scores of -1.3 and -1.9, respectively, owing to increases that occurred over 3 years of treatment in the original trials. After 5 years of treatment in FLEX, patients treated with alendronate had either the same or increased BMD at the hip, femoral neck, and lumbar spine compared with BMD decreases for the discontinuation (placebo) group. However, the decreases in the discontinuation group were smaller than would have been expected in individuals of the same age who had not previously received osteoporosis treatment. Differences between the pooled alendronate and the placebo groups were significant for total body BMD and BMD at the hip, femoral neck, and trochanter ($P < 0.001$).

At 5 years, the risk of clinical vertebral fractures was significantly less in women who continued to receive alendronate (2.4% vs. 5.3% for placebo), but rates for nonvertebral fractures (18.9% vs. 19%) and morphometric vertebral fractures (11.3% vs. 9.8%) were not significantly different between study groups.

Alendronate Weekly Dosing Trial

A randomized, double-blind, multinational, noninferiority trial to compare BMD changes for weekly versus daily alendronate dosing enrolled 1,258 women (42 to 95 years of age) with postmenopausal osteoporosis.[13,14] Alendronate 35 mg twice weekly and alendronate 70 mg weekly dosages were found to be noninferior to alendronate 10 mg daily for effects on BMD at 1 and 2 years. The mean increases from baseline in lumbar spine BMD at 2 years were 7.0%, 6.8%, and 7.4%, respectively, for the twice-weekly, once-weekly, and daily dosages. The 3 doses also produced similar reductions in bone turnover markers (urinary cross-linked *N*-telopeptide of type I collagen [NTx] and serum bone-specific alkaline phosphatase [BSAP]). Based on these results, the alendronate 70 mg once-weekly regimen was approved for the treatment of postmenopausal osteoporosis.

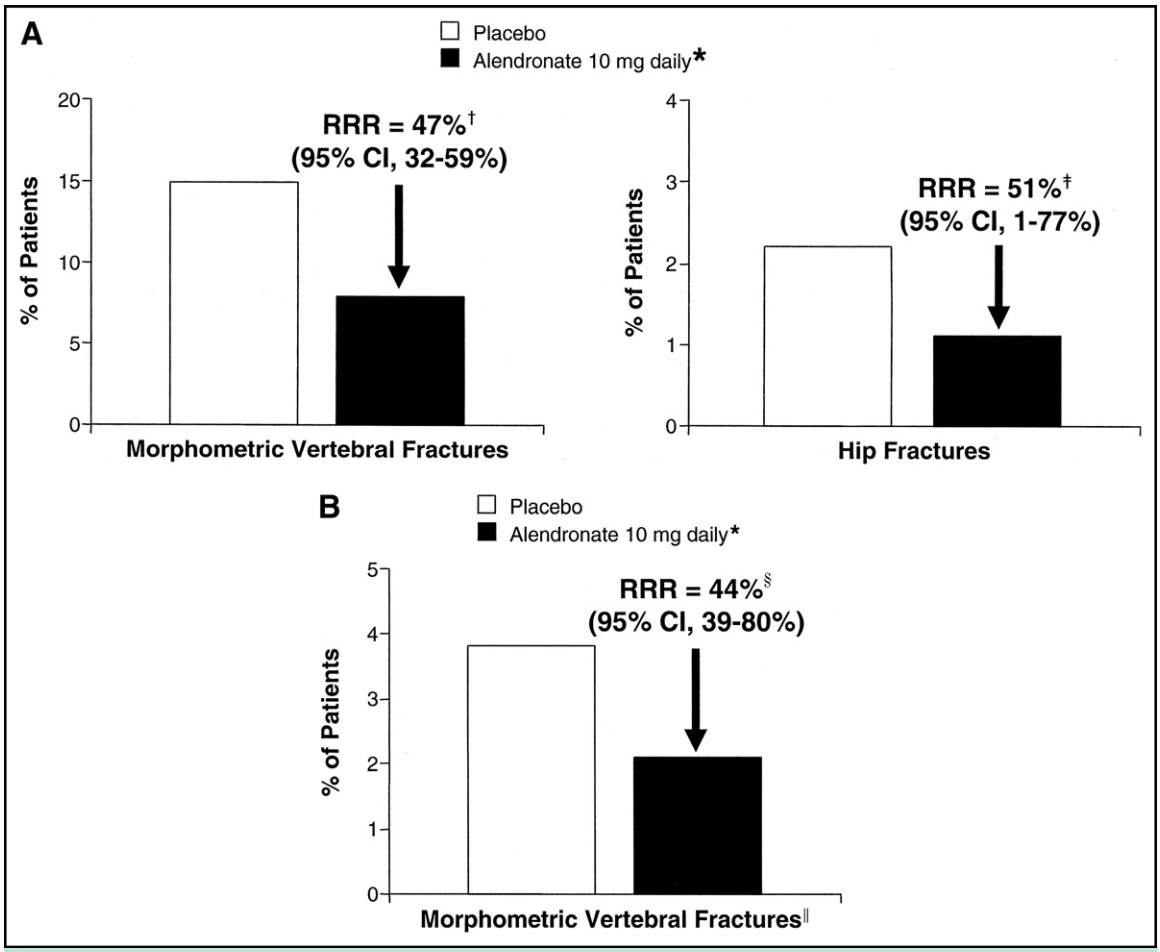

Figure 1 Rate of fractures in postmenopausal women receiving alendronate or placebo in (*A*) Fracture Intervention Trial (FIT)–1 after 3 years and (*B*) FIT-2 after a mean of 4.2 years. CI = confidence interval; RRR = relative risk reduction. *Alendronate 5 mg/day for the first 2 years of study. †P <0.001 vs. placebo; ‡P = 0.047 vs. placebo; §P = 0.002 vs. placebo. ‖Morphometric fractures defined as fractures diagnosed by a clinician. (Data from *Lancet*[10] and *JAMA*.[11])

RISEDRONATE

Vertebral Efficacy with Risedronate Therapy

Risedronate was studied in 2 efficacy-focused Vertebral Efficacy with Risedronate Therapy (VERT) trials. These pivotal trials included women aged <85 years who had entered menopause ≥5 years before the study.[15,16] One of the trials, VERT-NA, was conducted in North America and included women (mean age, 69 years) who had ≥2 vertebral fractures or 1 vertebral fracture and low lumbar spine BMD.[15] The other trial, VERT-MN (multinational),[16] was conducted in Europe and Australia and included women (mean age, 71 years) who had ≥2 vertebral fractures. Both were double-blind, placebo-controlled, multicenter trials. Initially, subjects (2,458 in VERT-NA and 1,226 in VERT-MN) were randomized to treatment with daily oral risedronate 5 mg or 2.5 mg or to placebo. However, in both studies, the risedronate 2.5-mg group was discontinued before completion of these 3-year trials because data from other trials indicated that this dose was less effective than the 5-mg dose. All study participants received a calcium supplement (1,000 mg/day) and cholecalciferol if serum vitamin D levels were low at baseline.

Over 3 years of therapy in the VERT-NA trial,[15] in which the mean lumbar spine T-score was −2.4 for the 3 treatment groups, vertebral and nonvertebral fractures were significantly reduced with risedronate 5 mg/day compared with placebo (Figure 2A). Vertebral fractures were reduced by 41% (11.3% vs. 16.3%, respectively; P = 0.003), and nonvertebral fractures were reduced by 39% (5.2% vs. 8.4%; P = 0.02). BMD increased significantly (P <0.05) from baseline in the risedronate group, by 5.4% at the lumbar spine, 1.6% at the femoral neck, and 3.3% at the femoral trochanter.

In the smaller VERT-MN trial,[16] which included older women with lower T-scores (mean lumbar spine T-scores ranging from −2.7 to −2.8 for the 3 treatment groups), a greater proportion of the women had fractures during the trial. New vertebral and nonvertebral fractures were both reduced by risedronate 5 mg/day. The reduction for vertebral fractures was significant compared with placebo (18%

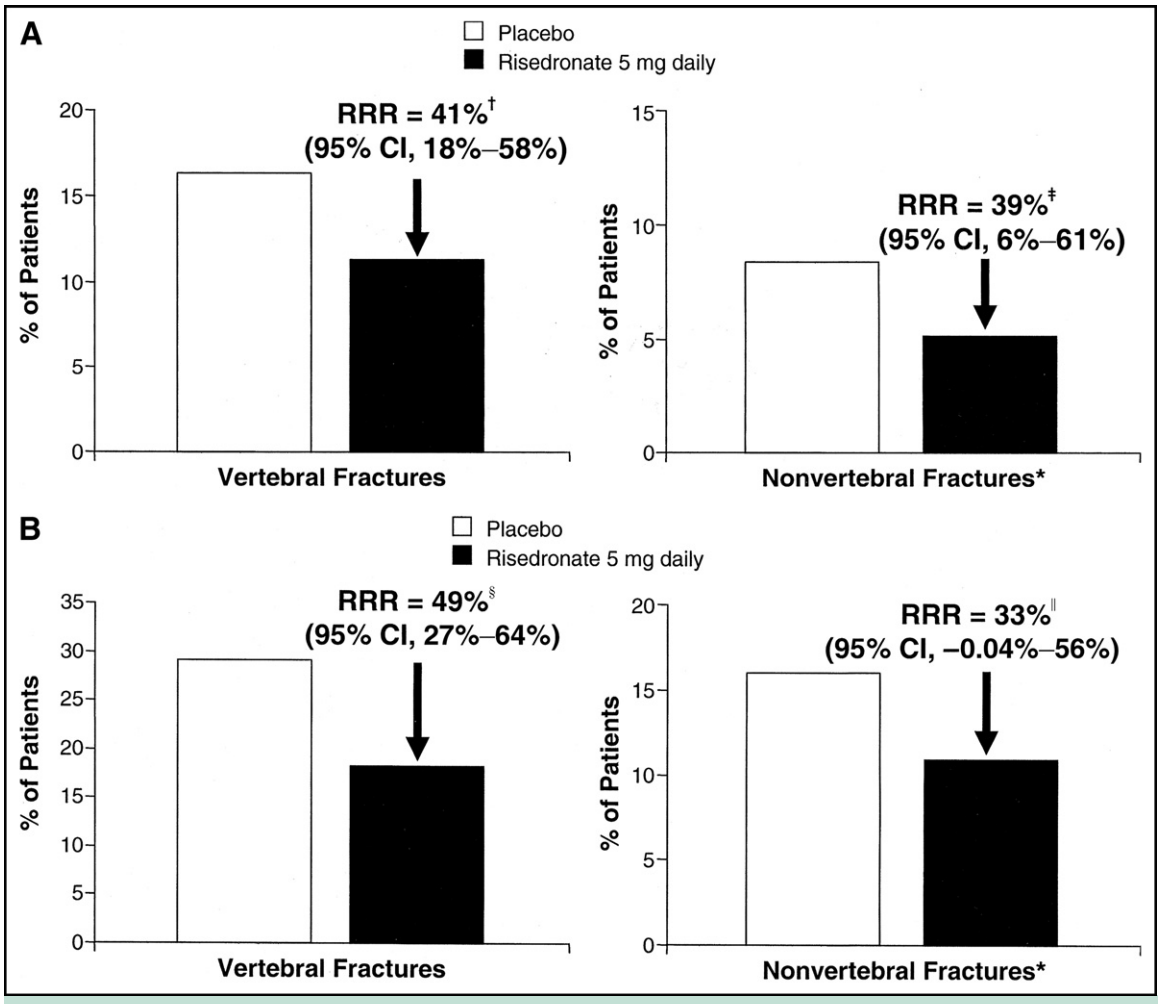

Figure 2 Rate of fractures in postmenopausal women treated with risedronate 5 mg or placebo over 3 years of treatment in the (*A*) Vertebral Efficacy with Risedronate Therapy (VERT)–North American (VERT-NA) and (*B*) VERT-Multinational (VERT-MN) trials. *P*-values from log-rank test. *Defined as fracture of the clavicle, humerus, wrist, pelvis, hip, or leg, regardless of trauma. †$P = 0.003$ vs. placebo; ‡$P = 0.02$ vs. placebo; §$P < 0.001$ vs. placebo; ‖$P = 0.063$ vs. placebo. CI = confidence interval; RRR = relative risk reduction. (Data from *JAMA*[15] and *Osteoporos Int.*[16])

vs. 29%; 49% reduction; $P < 0.001$) (Figure 2B). At 3 years, there were significant treatment differences in BMD, of 5.9% at the spine and 6.4% at the femoral trochanter (both $P < 0.001$).

VERT-MN Extension Trials. Double-blind treatment of women from VERT-MN[17] was continued for another 2 years with risedronate 5 mg/day (n = 135) and placebo (n = 130).[17] The risk for new vertebral fractures was significantly reduced with risedronate treatment in years 4 and 5 compared with the first 3 years (59% vs. 49%; $P = 0.01$). Increases in spine and hip BMD reported for the risedronate group during the first 3 years were maintained or increased with 2 subsequent years of treatment. This study showed that risedronate's effects on vertebral fracture and BMD over 3 years are maintained with a further 2 years of treatment. A small subgroup from this initial extension trial received an additional 2 years of risedronate treatment, and the results were similar, with maintenance of antifracture and BMD effect for up to 7 years.[18]

Hip Intervention Program Trial

The randomized, double-blind, placebo-controlled Hip Intervention Program (HIP) trial enrolled 5,445 women 70 to 79 years of age (mean age, 74 years) who had osteoporosis (femoral neck BMD T-score < -4, or < -3 with a nonskeletal risk factor for hip fracture, such as poor gait or a propensity to fall) and 3,886 women ≥80 years of age (mean age, 83 years) recruited primarily on the basis of clinical risk factors and not low BMD (criteria: ≥1 nonskeletal risk factor for hip fracture or low femoral neck BMD [T-score < -4 or < -3 with a hip-axis length ≥11.1 cm]).[19] Patients were randomized to receive oral risedronate (2.5 or 5.0 mg daily) or placebo for 3 years, and the primary end point was occurrence of hip fracture. The overall incidence of hip fracture for patients receiving

risedronate was 2.8%, versus 3.9% in those receiving placebo (relative risk reduction [RRR], 30%; $P = 0.02$). In the group of subjects with confirmed osteoporosis (70 to 79 years old), the incidence of hip fracture was 1.9% in patients receiving risedronate, compared with 3.2% for the placebo group (RRR, 40%; $P = 0.009$). In the group of subjects selected primarily on the basis of nonskeletal risk factors (those ≥80 years of age), the incidence of hip fracture was 4.2% for the risedronate group, versus 5.1% for the placebo group ($P = 0.35$). Thus, risedronate significantly reduced the risk for hip fracture in elderly women with confirmed osteoporosis but not in elderly women selected primarily on the basis of risk factors other than low BMD.

Risedronate Once-Weekly and Once-Monthly Dosing Studies

A 2-year randomized, double-blind, noninferiority (bridging) study was done to compare daily oral risedronate 5 mg/day with risedronate 35 and 50 mg weekly in 1,127 postmenopausal women ≥50 years of age with osteoporosis.[20,21] At 12 months,[20] lumbar spine BMD was noninferior for all between-group comparisons and had increased by a mean of 4.0% in the 5-mg/day treatment group and by means of 3.9% and 4.2% in the 35-mg and 50-mg weekly treatment groups, respectively. Over 2 years,[21] the incidence of new vertebral fractures (2.9%, 1.5%, and 1.7%, respectively) was not significantly different among these treatment groups. Increases in BMD and reductions in bone turnover markers (NTx/creatinine ratio and BSAP) were likewise not significantly different. As a result of these findings, the 35-mg weekly dose was approved for the treatment of postmenopausal osteoporosis.

A subsequent noninferiority study assessed the efficacy of risedronate 5 mg/day versus 150 mg once per month.[22] This multinational, double-blind, randomized trial involved 1,294 women aged ≥50 years with postmenopausal osteoporosis. At 1 year, lumbar spine BMD was increased by 3.4% in the daily treatment group, compared with 3.5% in the monthly treatment group. Reductions in bone turnover markers (NTx/creatinine ratio, serum cross-linked *C*-telopeptide of type I collagen [CTx], and BSAP) were also similar in both groups. Based on these data, the 150-mg monthly dose was approved for the treatment of postmenopausal osteoporosis.

ORAL IBANDRONATE

Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe

The 3-year efficacy of oral ibandronate in postmenopausal women with osteoporosis was established in the Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe (BONE), a double-blind, placebo-controlled, multicenter study that assessed 2 dosing regimens: ibandronate 2.5 mg/day (daily dosing group) and ibandronate 20 mg every other day for 12 doses every 3 months (intermittent dosing group).[23] A total of 2,946 women, 55 to 80 years of age (mean age, 69 years) and ≥5 years postmenopause, with 1 to 4 prevalent vertebral fractures and a T-score of −2 to −5 in ≥1 vertebra, were randomized to treatment. All participants received daily supplementation with calcium 500 mg and vitamin D 400 IU.

The primary end point was new morphometric vertebral fractures. After 3 years, new morphometric vertebral fractures were significantly reduced in the 2.5-mg/day ibandronate groups by 52% compared with the placebo group (4.7% vs. 9.6%; $P = 0.0001$) (Figure 3) and by 50% compared with placebo in the intermittent group (4.9% vs. 9.6%; $P = 0.0006$ [data not shown]).[23] Clinical vertebral fractures were also significantly reduced, by 49% in the 2.5-mg/day group compared with the placebo group. The incidence of nonvertebral fractures was not significantly reduced (placebo 8.2% vs. daily ibandronate 9.1%). Lumbar spine BMD was increased by 6.5% in the daily ibandronate group, and hip BMD was increased by 3.4%.

Monthly Ibandronate Bridging Study

During a 2-year, multicenter, double-blind, noninferiority bridging study, the Monthly Oral Ibandronate in Ladies (MOBILE) 2-year extension, monthly oral ibandronate 150 mg was shown to increase lumbar spine and total hip BMD significantly ($P < 0.05$) more than daily ibandronate 2.5 mg in postmenopausal women with osteoporosis.[24] The 150-mg once-monthly dose produced consistently greater reductions in the bone turnover marker serum CTx compared with the other 2 dosing regimens. As a result of these findings, the 150-mg once-monthly dose of ibandronate was approved for the treatment of postmenopausal osteoporosis.

INTRAVENOUS IBANDRONATE

Dosing Intravenous Administration Trial

In a double-blind, noninferiority, international multicenter trial (Dosing Intravenous Administration [DIVA] trial) that included 1,395 women, intermittent injections of ibandronate were compared with oral dosing for effects on BMD.[25] In this trial, women 55 to 80 years of age (mean age, 66 years) with osteoporosis and ≥5 years postmenopause were randomized to treatment with 2-mg ibandronate injections every 2 months plus oral placebo, 3-mg ibandronate injections every 3 months plus oral placebo, or 1 of 2 groups receiving oral ibandronate 2.5 mg/day plus placebo injections every 2 or every 3 months. All participants received daily supplementation with calcium 500 mg and vitamin D 400 IU.

At 1 year, mean increases in lumbar spine BMD (primary end point) were 5.1%, 4.8%, and 3.8% for the every-2-months injection, the every-3-months injection, and both oral treatment groups, respectively.[25] The BMD changes in both intravenous groups were significantly greater ($P < 0.001$) than in the oral treatment group. Also, both intravenous

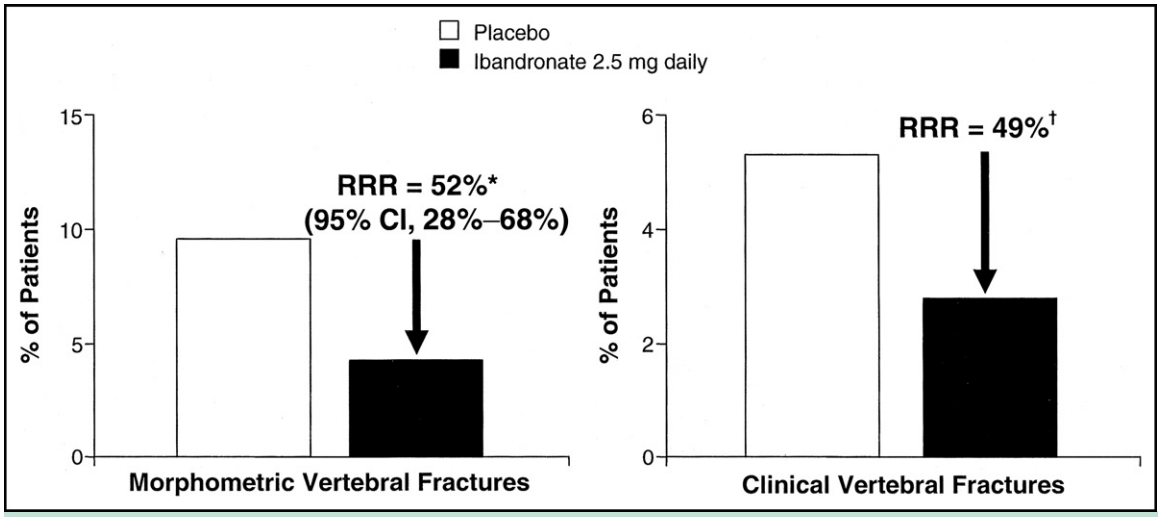

Figure 3 Rate of vertebral fractures (as estimated by life-table analysis) over 3 years in postmenopausal women treated with oral ibandronate 2.5 mg daily or placebo in the Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe (BONE) trial. $^{*}P = 0.0001$ vs. placebo; $^{\dagger}P = 0.0117$ vs. placebo. CI = confidence interval; RRR = relative risk reduction. (Adapted from *J Bone Miner Res.*[23])

groups had significantly greater ($P < 0.05$) changes in total hip and trochanter BMD, and the 3-month injection group had significantly greater changes in femoral neck BMD compared with the oral treatment groups. All treatment groups had similar reductions in the bone turnover marker serum CTx. Based on these data, the ibandronate quarterly injection (3 mg every 3 months) was approved for the treatment of postmenopausal osteoporosis.

ZOLEDRONIC ACID

Health Outcomes and Reduced Incidence With Zoledronic Acid Once Yearly–Pivotal Fracture Trial

The Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON)–Pivotal Fracture Trial[26] was a double-blind, placebo-controlled, multicenter international trial designed to assess the efficacy of a single 15-minute infusion of zoledronic acid 5 mg every 12 months over 3 years for reducing new vertebral fractures and hip fractures. The patients were postmenopausal women 65 to 89 years of age (mean age, 73 years) with either a T-score ≤ -2.5 at the femoral neck with or without evidence of an existing vertebral fracture or a T-score ≤ -1.5 with radiologic evidence of ≥ 2 mild vertebral fractures or 1 moderate vertebral fracture. These women were divided into 2 treatment strata based on whether or not they were taking allowed osteoporosis medications at the time of randomization. Most of the patients were in stratum 1, which included only women who had not previously been treated with other osteoporotic medications, or those who had previously used bisphosphonates but met prespecified washout criteria. A total of 7,765 women were randomized to active treatment or placebo, and all patients received daily supplementation with calcium 1,000 to 1,500 mg and vitamin D 400 to 1,200 IU.

Primary end points in this trial were the 3-year incidence of morphometric vertebral fractures and of hip fractures. Morphometric vertebral fractures were significantly reduced, by 70%, with once-yearly zoledronic acid infusions compared with placebo (3.3% vs. 10.9%, respectively; $P < 0.001$), and hip fractures were also significantly reduced, by 41% (1.4% vs. 2.5%; $P = 0.002$) (Figure 4).[26] The secondary end points of nonvertebral fractures, all clinical fractures, clinical vertebral fractures, and multiple morphometric vertebral fractures were also significantly ($P < 0.001$) reduced for the zoledronic acid group compared with the placebo group. BMD at the total hip, lumbar spine, and femoral neck were increased significantly, by 6.0%, 6.7%, and 5.1%, respectively, compared with placebo ($P < 0.001$ for all comparisons).

HORIZON–Recurrent Fracture Trial

A separate trial of zoledronic acid 5 mg (the HORIZON–Recurrent Fracture Trial) was conducted in patients who had undergone surgical repair of a low-trauma hip fracture within the previous 90 days[27]—the first such study in this undertreated population. In this double-blind, multinational trial, 2,127 men (24%) and women (76%) ≥ 50 years of age (mean age, 75 years) were randomized to yearly placebo or zoledronic acid 5-mg infusions and were monitored for a median of 1.9 years. Because of the prevalence of vitamin D deficiency, most patients received a loading dose of vitamin D 14 days before the first infusion, and all patients received calcium 1,000 to 1,500 mg and vitamin D 800 to 1,200 IU each day.

The primary end point, any new clinical fracture, occurred in 92 (8.6%) of patients treated with zoledronic acid and 139 (13.9%) of patients in the placebo group, a risk

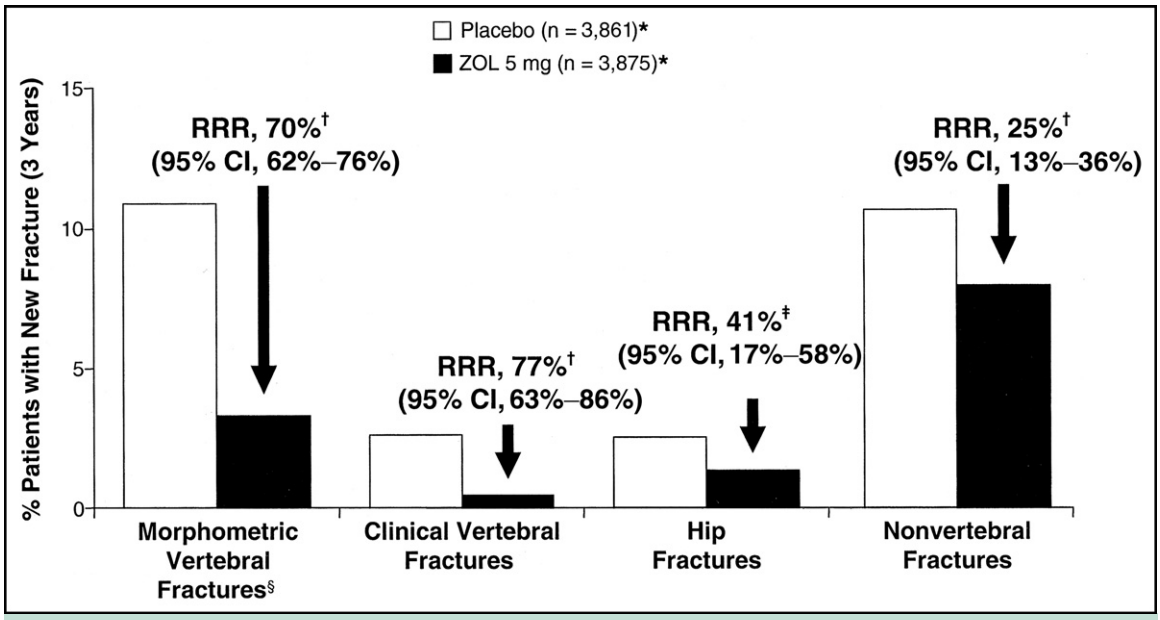

Figure 4 Rates of fractures over 3 years in postmenopausal women treated with zoledronic acid 5 mg (ZOL) or placebo infusions every 12 months in the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON)–Pivotal Fracture Trial. Values for hip fractures, clinical vertebral fractures, and nonvertebral fractures are cumulative event rates based on Kaplan-Meier estimates at month 36. *P*-values are based on an adjusted logistic-regression analysis. *A total of 14 patients in the zoledronic acid group and 15 in the placebo group were excluded from all analyses because the participation of their clinical center was terminated, owing to issues associated with reliability of data. †$P < 0.001$ vs. placebo; ‡$P = 0.002$ vs. placebo. §Includes stratum 1 patients only (no concomitant therapy). CI = confidence interval; RRR = relative risk reduction. (Adapted from *N Engl J Med.*[26])

reduction of 35% ($P = 0.001$). The rates of new clinical vertebral fractures were 1.7% for zoledronic acid and 3.8% for placebo, a risk reduction of 46% ($P = 0.02$), and the respective rates of new nonvertebral fractures were 7.6% and 10.7%, a 27% risk reduction ($P = 0.03$). The rates of new hip fractures were 2.0% for zoledronic acid and 3.5% for placebo, a 30% risk reduction ($P = 0.18$). The incidence of all-cause mortality was 9.6% in the zoledronic acid group and 13.3% in the placebo group (28% reduction; $P = 0.01$).

SUMMARY

The efficacy of bisphosphonates for the reduction of fractures in patients with osteoporosis has been shown in many large controlled clinical trials. Extension studies have further shown in some cases, and at some sites, that bisphosphonates can persist in their efficacy for longer terms (7 to 10 years), with strong safety profiles. Bridging studies have been done to assess the efficacy of longer dosing intervals, which take advantage of the retention and recycling of bisphosphonates in the bone and have the potential to help improve patient compliance and adherence during long-term treatment. These bridging trials have shown that longer dosing intervals result in equivalent benefits with respect to effect on BMD. The availability of a once-yearly intravenous therapy, zoledronic acid 5 mg, may yield further improvements in compliance and outcomes in the growing population of patients with osteoporosis.

ACKNOWLEDGMENT

The authors thank BioScience Communications, New York, New York for editorial assistance in the development of the manuscript.

AUTHOR DISCLOSURES

The author of this article has disclosed the following industry relationships:

John P. Bilezikian, MD, has worked as a paid consultant to Eli Lilly and Company, Merck & Co., Inc., Novartis Pharmaceuticals Corporation, Procter & Gamble Pharmaceuticals, Inc., and sanofi-aventis and has received research/grant support from GlaxoSmithKline, NPS Allelix Corp., Procter & Gamble Pharmaceuticals, Inc., and Radius Health, Inc.

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