

Effects of Risedronate Treatment on Vertebral and Nonvertebral Fractures in Women With Postmenopausal Osteoporosis

A Randomized Controlled Trial

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DECLINING ESTROGEN LEVELS at menopause result in increased bone turnover and a loss of bone mass, with subsequent increases in bone fragility and the risk of bone fracture. Vertebral fracture, in particular, is a common consequence of osteoporosis and may be considered the hallmark fracture for osteoporosis in postmenopausal women.¹ Because of the high frequency of vertebral fractures in patients with postmenopausal osteoporosis, clinical trials of osteoporosis therapies now typically assess the effects of treatment on vertebral fracture incidence as the primary end point. Prevention of nonvertebral fractures is another important goal

See also Patient Page.

Context Risedronate, a potent bisphosphonate, has been shown to be effective in the treatment of Paget disease of bone and other metabolic bone diseases but, to our knowledge, it has not been evaluated in the treatment of established postmenopausal osteoporosis.

Objective To test the efficacy and safety of daily treatment with risedronate to reduce the risk of vertebral and other fractures in postmenopausal women with established osteoporosis.

Design, Setting, and Participants Randomized, double-blind, placebo-controlled trial of 2458 ambulatory postmenopausal women younger than 85 years with at least 1 vertebral fracture at baseline who were enrolled at 1 of 110 centers in North America conducted between December 1993 and January 1998.

Interventions Subjects were randomly assigned to receive oral treatment for 3 years with risedronate (2.5 or 5 mg/d) or placebo. All subjects received calcium, 1000 mg/d. Vitamin D (cholecalciferol, up to 500 IU/d) was provided if baseline levels of 25-hydroxyvitamin D were low.

Main Outcome Measures Incidence of new vertebral fractures as detected by quantitative and semiquantitative assessments of radiographs; incidence of radiographically confirmed nonvertebral fractures and change from baseline in bone mineral density as determined by dual x-ray absorptiometry.

Results The 2.5 mg/d of risedronate arm was discontinued after 1 year; in the placebo and 5 mg/d of risedronate arms, 450 and 489 subjects, respectively, completed all 3 years of the trial. Treatment with 5 mg/d of risedronate, compared with placebo, decreased the cumulative incidence of new vertebral fractures by 41% (95% confidence interval [CI], 18%-58%) over 3 years (11.3% vs 16.3%; $P = .003$). A fracture reduction of 65% (95% CI, 38%-81%) was observed after the first year (2.4% vs 6.4%; $P < .001$). The cumulative incidence of nonvertebral fractures over 3 years was reduced by 39% (95% CI, 6%-61%) (5.2% vs 8.4%; $P = .02$). Bone mineral density increased significantly compared with placebo at the lumbar spine (5.4% vs 1.1%), femoral neck (1.6% vs -1.2%), femoral trochanter (3.3% vs -0.7%), and midshaft of the radius (0.2% vs -1.4%). Bone formed during risedronate treatment was histologically normal. The overall safety profile of risedronate, including gastrointestinal safety, was similar to that of placebo.

Conclusions These data suggest that risedronate therapy is effective and well tolerated in the treatment of women with established postmenopausal osteoporosis.

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of treatment because of the pain and disability associated with these fractures.

Several therapies have demonstrated antifracture efficacy in the treatment of established postmenopausal

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osteoporosis. Hormone replacement therapy reduced the occurrence of vertebral fracture in a small, prospective trial,² and a prospective cohort study supports the usefulness of hormone replacement therapy in reducing the progression of disease, even in older women.³ However, sustained benefit requires long-term use of hormones, and few women accept long-term treatment due to poor tolerability and fear of breast cancer.^{4,5} Both raloxifene and calcitonin have been shown to modestly increase bone mineral density (BMD) and decrease the incidence of vertebral fracture; however, neither therapy has demonstrated significant effects in reducing nonvertebral fractures.⁶⁻⁸ Other bisphosphonates have demonstrated efficacy in prevention of vertebral fracture, although the interpretation of the fracture results in these studies is complicated by the pooling of dosage groups,⁹ changing of dosage during the study,¹⁰ and analysis of subpopulations.¹¹ Although alendronate reduced the incidence of all clinical fractures in a population of patients with a history of vertebral fractures,¹⁰ a recent study in more than 4000 subjects with low BMD and no history of vertebral fracture failed to demonstrate this benefit, except in a subpopulation of women with low hip bone density.¹² Gastrointestinal tract adverse effects are a concern with some bisphosphonates.¹³⁻¹⁵ Although the incidence of such adverse effects has been low, upper gastrointestinal tract adverse events such as erosive esophagitis have been reported.^{14,15}

Risedronate (chemical name, [1-hydroxy-2-(3-pyridinyl) ethylidene] bis[phosphonic acid] monosodium salt), a pyridinyl bisphosphonate with potent antiresorptive activity, has been shown to be effective for the treatment of Paget disease of bone^{16,17} and multiple myeloma,^{18,19} and for the prevention of bone loss in early postmenopause.²⁰ The present study was designed to test the efficacy of daily risedronate treatment in reducing the incidence of vertebral and other fractures in postmenopausal women with

a history of vertebral fracture and to evaluate the safety of risedronate therapy in these patients.

METHODS

Protocol

This randomized, double-blind, placebo-controlled, parallel-group study was conducted at 110 study centers in North America between December 1993 and January 1998. Study centers included office-based practices, academic research centers, and regional osteoporosis clinics. All subjects gave written informed consent before enrollment into the study, which was conducted according to the tenets of the Declaration of Helsinki and approved by the appropriate institutional review boards.

Ambulatory women were eligible for the study if they were no older than 85 years, if 5 years had elapsed since natural or surgical menopause, and if they had either 2 or more radiographically identified vertebral fractures (T4-L4, inclusive) or 1 vertebral fracture and low lumbar-spine (L1-L4) BMD (defined as ≤ 0.83 g/cm² [Hologic instrument] or ≤ 0.94 g/cm² [Lunar instrument]). These values represent a T score of -2 (2 SDs below the mean for young adults). Women were excluded if they had conditions that might interfere with the evaluation of spinal bone loss, or if they had received drugs known to affect bone metabolism (such as calcitonin, calcitriol or cholecalciferol supplements within 1 month prior to study entry; anabolic steroids, estrogen or estrogen-related drugs, or progestins within 3 months; or bisphosphonates, fluoride, or subcutaneous estrogen implants within 6 months). Subjects were not excluded specifically because of previous or active gastrointestinal illness or because of concomitant use of aspirin or nonsteroidal anti-inflammatory agents.

Assignment

Participants were stratified based on the number of baseline vertebral fractures (stratum 1, subjects with 1 vertebral fracture and low baseline BMD; stratum 2, subjects with ≥ 2 baseline vertebral frac-

tures) and randomly assigned (block size of 3 within each stratum at each study center) to 1 of 3 treatment groups: risedronate, 5 mg/d; risedronate, 2.5 mg/d; or placebo. The randomization schedule was generated by Quintiles Inc (Durham, NC) using SAS version 6.07 (SAS Inc, Cary, NC). Treatment assignments were based on a randomization number issued to each patient after completion of screening procedures.

Blinding

A number of procedures were in place to maintain blinding throughout the study. During the trial, the randomization schedule was held by a clinical research organization (Covance, Princeton, NJ). Covance staff, the investigators, and other research personnel remained blinded to the treatment assignments in the placebo and 5-mg risedronate treatment groups when the 2.5-mg risedronate arm was discontinued. Treatment assignments could be released to the investigators only for reasons of patient safety. To protect the blinding, the placebo and risedronate tablets were physically indistinguishable, and study medication was provided in coded containers labeled with dosing instructions.

Treatment

Subjects were instructed to take the study drug once daily on an empty stomach, 30 to 60 minutes before breakfast, with water, and to remain in an upright position for 1 hour after dosing. All participants received a calcium supplement equivalent to 1000 mg of elemental calcium daily, to be taken with the evening meal. Subjects with low serum 25-hydroxyvitamin D levels at baseline (< 40 nmol/L) also received cholecalciferol supplementation (up to 500 IU/d).

Outcome Assessments

Vertebral Fractures. The incidence of new vertebral fractures (fractures in previously normal vertebrae) was expressed as the proportion of subjects with at least 1 incident fracture over 3 years of study. New and worsening ver-

tebral fractures (fractures in previously normal vertebrae and worsening fractures in already fractured vertebrae) were also examined. The sample size of approximately 2400 was based on an expected annual new vertebral fracture incidence of 10% in the placebo group. Assuming a patient withdrawal rate of 50% over 3 years, the study was designed to have at least 90% power to detect a 40% reduction in vertebral fracture risk, with a 2-sided significance level of $P = .05$.

Lateral thoracic and lumbar spine radiographs were taken at baseline and annually throughout the study. Subjects were enrolled based on a visual assessment of prevalent fractures (T4-L4). For this assessment, a vertebra was considered fractured if the ratio of the anterior or middle vertebral body height to the posterior vertebral body height was 0.8 or less. Quantitative²¹ and semiquantitative assessments²² were used to identify both prevalent (baseline) and incident vertebral fractures for the purposes of the efficacy determination. An incident new vertebral fracture was defined quantitatively as a loss of 15% or more in the anterior, posterior, or middle vertebral height in a vertebra that was normal at baseline and semiquantitatively as a change from grade 0 (normal) to grades 1 (mild), 2 (moderate), or 3 (severe). A worsening vertebral fracture was recorded if there was a change of 4 mm or more in vertebral height since the previous radiograph or a change in grade in a previously fractured vertebra. An independent radiologist adjudicated discrepancies between the quantitative and semiquantitative methods.²³ The radiologists remained blinded to treatment assignment while performing all vertebral fracture assessments.

Bone Mineral Density. Bone mineral density was measured by dual x-ray absorptiometry at baseline and at 6-month intervals throughout the study using Lunar (Lunar Corporation, Madison, Wis) or Hologic (Hologic Inc, Waltham, Mass) densitometers. Scans were analyzed at a central location (Department of Radiology, University of California, San Francisco). Standard-

ized lumbar spine BMD was calculated at baseline to correct for differences in instrumentation.^{24,25} Femoral neck BMD values obtained using Lunar instruments were adjusted to make them comparable to those obtained using Hologic instruments.²⁴

Other Efficacy Measurements. Radiographically confirmed nonvertebral fractures (defined as fractures of the clavicle, humerus, wrist, pelvis, hip, or leg, whether or not associated with trauma) were recorded throughout the study.

Biochemical markers of bone turnover were assessed in subjects enrolled at a subset of the study centers. Urine was collected for 2 hours after the overnight void on the morning of the office visit, and samples were stored at -70°C until analyzed. Stored samples were analyzed in batches over the course of the study. These measurements were performed at a central laboratory (Quest Diagnostics Inc, San Juan Capistrano, Calif). Bone-specific alkaline phosphatase was determined using the Tandem R-Ostase immunoradiometric assay (Hybritech Inc, San Diego, Calif), and deoxypyridinoline-creatinine ratio was measured by high-pressure liquid chromatography.

Safety Evaluations

Each participant received a physical examination at baseline and at the end of the study. Vital signs and standard hematology and clinical chemistry tests were performed at regular study visits, and adverse events were recorded. Endoscopy was performed at the discretion of the investigator in subjects who reported gastrointestinal complaints.

At selected study centers, iliac crest bone biopsy samples were obtained at baseline and posttreatment following double tetracycline labeling. Histologic and histomorphometric assessments of these samples were performed by a single center in Aarhus, Denmark (E.F.E.). For general bone safety purposes, selected qualitative and quantitative observations are reported here. A full report of these data will be the subject of a future publication.

Statistical Analyses

The planned duration of this study was 3 years. After the study was begun, data from other trials indicated that the 2.5-mg risedronate dose was less effective than the 5-mg dose, and the 2.5-mg risedronate treatment arm in this trial was discontinued by protocol amendment. Therefore, the prospectively defined primary analysis compared the 5-mg risedronate and placebo groups at the 5% significance level. Efficacy analyses were performed on an intention-to-treat basis. In order to facilitate statistical analyses where center was included as a blocking or stratification factor, the 110 investigator sites were pooled by geographic region to form 13 pooled centers prior to unblinding.

At baseline, continuous variables were compared by analysis of variance (ANOVA) with treatment, pooled center, and stratum as factors. Discrete variables were compared by the Cochran-Mantel-Haenszel test, stratified by pooled center and stratum.

For the analysis of fracture incidence (both vertebral and nonvertebral), the placebo and 5-mg risedronate groups were compared on the basis of time to first diagnosed fracture using a stratified log-rank test. A stratified Cox proportional hazards regression model was used to estimate the relative risk of fracture between the 5-mg risedronate and placebo groups. Fracture incidence was calculated using the Kaplan-Meier method.²⁶

Bone mineral density (percentage change from baseline) and bone turnover markers were analyzed by ANOVA. Nonparametric methods were used if model assumptions were not met.

RESULTS

Of approximately 9400 patients screened, lumbar spine radiographs were obtained for about 5800 patients, 35% of whom did not meet the radiologic criteria for study participation. A total of 2458 women met the entry criteria and were enrolled at 110 study centers in North America (FIGURE 1). All treatment groups had similar demographic

characteristics and BMD values at baseline (TABLE 1). Few subjects (9%) required cholecalciferol supplementation because of low baseline serum levels of 25-hydroxyvitamin D. The majority of subjects were white (96%). Across treatment groups, 1847 subjects (75.7%) completed 1 year of treatment. The 2.5-mg risedronate arm was discontinued by protocol amendment after the first year; 55% of subjects in the placebo group and 60% of subjects in the 5-mg risedronate group completed 3 years of treatment. There were no obvious differences between groups in the

reasons for patient withdrawal, and the most common reasons for voluntary withdrawals in all groups were lack of interest, transportation difficulties, and age-related problems (such as the illness of a spouse): these reasons accounted for 83% of all voluntary withdrawals. Examination of a number of parameters, including baseline number of vertebral fractures, lumbar spine T score, age, years since menopause, incidence of adverse events and of vertebral fractures during the trial, and use of concomitant medications, found only 1 apparent difference between patients

who withdrew and those who completed the study. Among patients withdrawing from the study, a substantially higher proportion of patients in the placebo group (19.6%) had incident vertebral fractures compared with the proportion of patients in the 5-mg risedronate group (10.6%). More than 85% of subjects in each treatment group took at least 80% of the study medication based on tablet counts.

Vertebral and Nonvertebral Fractures

The majority of subjects (86%) who experienced vertebral fractures had at least 1 fracture of a previously normal vertebra (a “new” fracture). Over 3 years, there was a statistically significant reduction of 41% (95% confidence interval [CI], 18%-58%) in the risk of new vertebral fractures in the 5-mg risedronate group compared with placebo ($P = .003$) (TABLE 2 and FIGURE 2). The Kaplan-Meier estimates of the incidence over 3 years were 11% in the 5-mg risedronate group and 16% in the placebo group. A significant reduction of 65% (95% CI, 38%-81%) in vertebral fracture risk (2.4% vs 6.4%; $P < .001$) was seen in the first year of treatment. Approximately 80% of the patients were randomized to stratum 2. This subgroup experienced a 43% reduction in new vertebral fractures over 3 years ($P = .003$). A similar pattern of response was seen when the proportion of subjects with new and worsening (ie, all incident deformities, whether in previously normal or already deformed vertebrae) vertebral fractures was examined, or when the data were examined using the last observation carried forward for all patients who withdrew. Data are available for the 2.5-mg risedronate group only for the first year of treatment; the effect observed with the 2.5-mg dose was smaller than that seen with the 5-mg dose of risedronate (data not shown).

The cumulative incidence of nonvertebral fractures over 3 years of treatment was lower by 39% (95% CI, 6%-61%) in the 5-mg risedronate group compared with placebo (5.2% vs 8.4%;

Figure 1. Study Profile and Patient Disposition

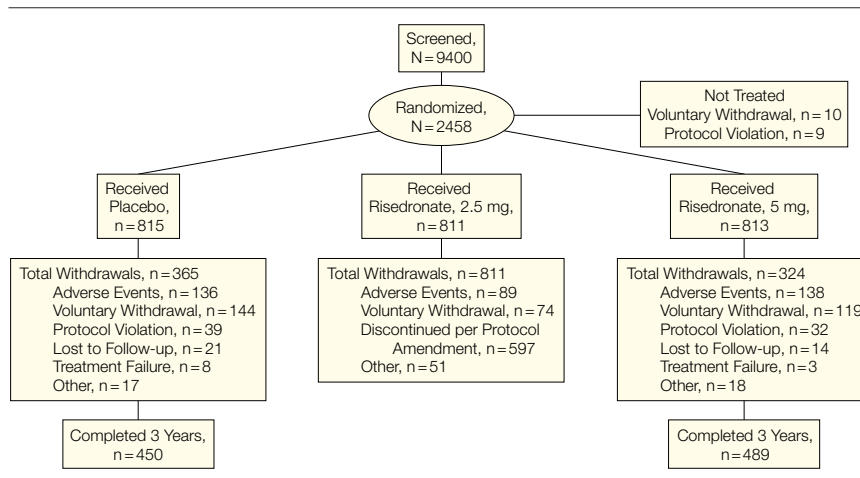


Table 1. Subject Baseline Characteristics*

| | Study Group | | |
|---|-------------------|------------------|----------------|
| | Placebo (n = 820) | Risedronate | |
| | | 2.5 mg (n = 817) | 5 mg (n = 821) |
| Age, y | 68 (7.2) | 69 (7.1) | 69 (7.7) |
| Time since menopause, y | 24 (10.0) | 24 (9.5) | 24 (10.1) |
| Mean height, cm | 159 (6.9) | 158 (7.0) | 158 (6.8) |
| Mean weight, kg | 67.0 (13.3) | 66.4 (13.3) | 66.5 (13.6) |
| Smokers | | | |
| Current or previous, No. (%) | 396 (48) | 412 (50) | 419 (51) |
| Never, No. (%) | 424 (52) | 405 (50) | 402 (49) |
| Subjects with prevalent vertebral fractures, No. (%)† | 639 (79) | 681 (85) | 645 (80) |
| Mean No. of vertebral fractures per patient | 2.3 (0.08) | 2.7 (0.09) | 2.5 (0.09) |
| Standardized lumbar spine BMD, mg/cm ² | 829 (164) | 839 (163) | 832 (158) |
| Mean lumbar spine T score | -2.4 (1.4) | -2.4 (1.4) | -2.4 (1.4) |
| Mean femoral neck BMD, g/cm ² | 0.602 (0.102) | 0.597 (0.103) | 0.593 (0.105) |
| Mean femoral neck T score | -2.6 (1.1) | -2.6 (1.1) | -2.7 (1.1) |

*BMD indicates bone mineral density. All data in parentheses are SD unless indicated otherwise.
†Based on the adjudicated fracture assessment.

$P = .02$) (FIGURE 3). The number of patients with fracture in the 5-mg risedronate and placebo groups, respectively, was 14 and 22 at the wrist, 12 and 15 at the hip and/or pelvis, 4 and 10 at the humerus, 4 and 8 at the leg, and 3 and 0 at the clavicle.

Bone Mineral Density

Over 3 years, subjects in the 5-mg risedronate group experienced significant increases in BMD from baseline at the lumbar spine (5.4%), femoral neck (1.6%), and femoral trochanter (3.3%); significant differences compared with baseline and placebo were seen within 6 months (FIGURE 4). The placebo group showed small but significant ($P < .05$) changes from baseline in BMD at the lumbar spine (1.1%), femoral neck (-1.2%), and femoral trochanter (-0.7%) over 3 years. At the midshaft of the radius, the 5-mg risedronate group experienced no change in BMD (0.2%), compared with a significant ($P < .05$) loss in the placebo group of -1.4%.

Markers of Bone Turnover

Bone turnover marker data were available from patients (775/2458 [32%]) at a subset of study centers. Bone-specific alkaline phosphatase levels declined with 5-mg risedronate treatment, reaching a nadir of -35% (median percentage change from baseline) in the

risedronate group at 6 months, compared with -12% in the placebo group (FIGURE 5). Values at the end of 3 years of treatment were -33% and -7%, respectively. Similar changes were seen in the deoxypyridinoline-creatinine ratio, which reached a nadir at 6 months of -38% in the 5-mg risedronate group compared with -8% in the placebo group and also rose by the end of the study to values of -26% and -1%, respectively (Figure 5).

Adverse Events

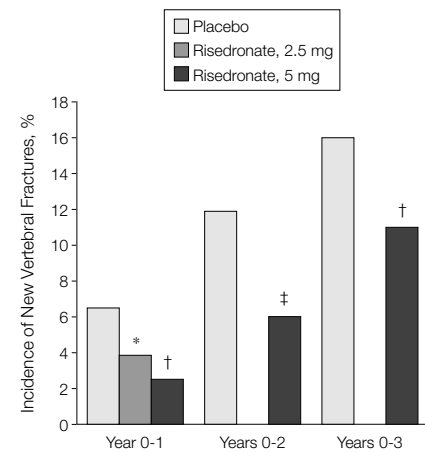
The overall incidence of adverse events was similar across treatment groups, as was the incidence of serious adverse events and the incidence of drug-related adverse events (TABLE 3). The proportion of subjects in the 5-mg risedronate group who withdrew from the study because of an adverse event was similar to that in the placebo group, whereas the proportion in the 2.5-mg risedronate group, which had a shorter exposure, was lower. Digestive system complaints were the most common adverse events associated with study discontinuance, accounting for 56 patients (42%) withdrawing due to adverse events in the placebo group, compared with 49 patients (36%) in the 5-mg risedronate group.

Most adverse events were reported at similar frequencies in the risedronate and placebo groups. Consistent with the

efficacy findings, bone fractures reported as adverse events occurred at a lower incidence in the 5-mg risedronate group than in the placebo group (13% vs 18%; $P = .009$). There were no significant biochemical changes observed in renal, hepatic, or hematologic parameters in any treatment group.

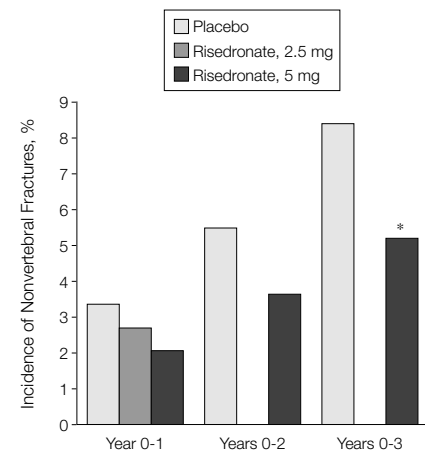
Overall, the incidence of upper gastrointestinal tract adverse events in the 5-mg risedronate group was similar to that in the placebo group, and most of these events were of mild-to-moderate

Figure 2. Incidence of New Vertebral Fractures by Groups Over Time



Asterisk indicates $P < .05$; dagger, $P < .01$; and double dagger, $P < .001$ vs placebo.

Figure 3. Incidence of Nonvertebral Fractures by Study Group Over Time



Asterisk indicates $P < .05$ vs placebo.

Table 2. Cumulative Incidence of Fractures

| Treatment Group by Time | No.* | Subjects With Incident Fracture, No. (%)† | Relative Risk (95% Confidence Interval)‡ | P Value§ |
|--------------------------------|------|---|--|----------|
| New vertebral fractures | | | | |
| Year 0-1 | | | | |
| Placebo | 660 | 42 (6.4) | | |
| Risedronate, 2.5 mg | 618 | 23 (3.8) | 0.54 (0.32-0.91) | .02 |
| Risedronate, 5 mg | 669 | 16 (2.4) | 0.35 (0.19-0.62) | <.001 |
| Years 0-3 | | | | |
| Placebo | 678 | 93 (16.3) | | |
| Risedronate, 5 mg | 696 | 61 (11.3) | 0.59 (0.43-0.82) | .003 |
| Nonvertebral fractures | | | | |
| Years 0-3 | | | | |
| Placebo | 815 | 52 (8.4) | | |
| Risedronate, 5 mg | 812 | 33 (5.2) | 0.6 (0.39-0.94) | .02 |

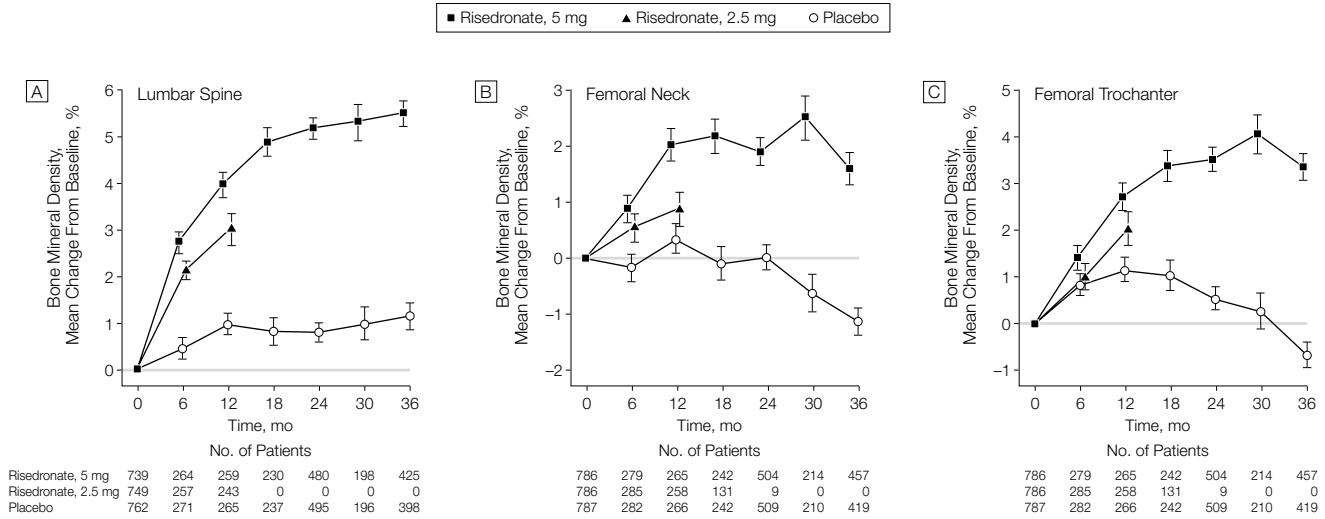
*For vertebral fracture assessments, the number of subjects is those with evaluable radiographs both at baseline and after treatment.

†Proportion is based on Kaplan-Meier estimate of the survival function.

‡Based on Cox regression model.

§Based on log-rank test.

Figure 4. Mean Percent Change From Baseline in Bone Mineral Density



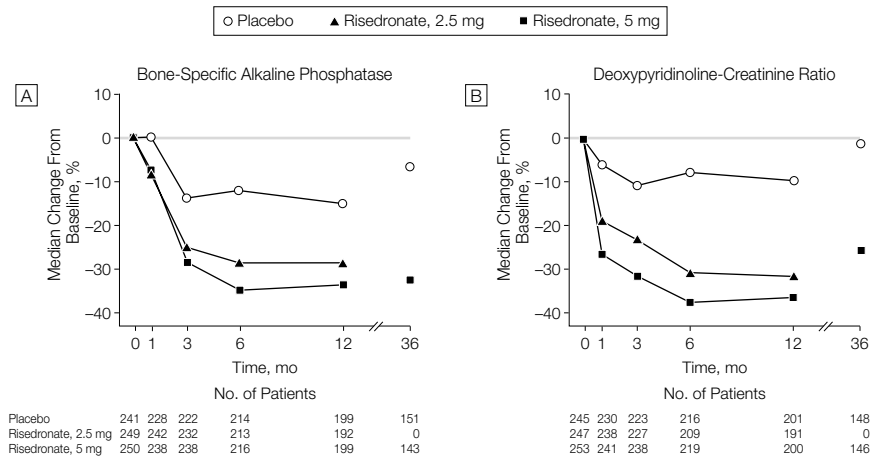
Error bars represent SEM. Measurements at 6, 12, 18, and 30 months were performed at a subset of study centers. In A, $P < .05$ vs baseline for all time points and groups except the placebo group at 6 months; $P < .05$ vs placebo for all time points in the 2.5-mg and 5-mg risedronate groups. In B, $P < .05$ vs baseline for all time points and groups except the placebo group between 0 and 24 months; $P < .05$ vs placebo for all time points in the 5-mg risedronate group and at 6 months for the 2.5-mg group. In C, $P < .05$ vs baseline for all time points and groups except the placebo group at 30 months; $P < .05$ vs placebo for all time points in the 5-mg risedronate group except 6 months.

severity. The most common upper gastrointestinal tract adverse events were dyspepsia, abdominal pain, and gastritis. The percentage of subjects (4.2%) in the 5-mg risedronate group who underwent gastrointestinal tract endoscopy after reporting gastrointestinal adverse events was similar to that in the placebo group (3.7%), and a similar proportion of subjects in each group undergoing endoscopy had some abnormal finding (85% and 83%, respectively). More cases of duodenitis were reported in the 5-mg risedronate group compared with placebo (9 vs 2), but there were fewer cases of duodenal ulcer in the 5-mg risedronate group (1 vs 3).

Bone Safety

A total of 62 pairs of biopsy samples (baseline and end-of-study samples from the same patient) were available from 31 subjects each in the placebo and the 5-mg risedronate groups. Histologic assessment revealed normal bone with no evidence of mineralization problems or marrow abnormalities in risedronate-treated subjects. Based on histomorphometric analyses, risedronate treatment reduced bone

Figure 5. Median Percentage Change From Baseline in Bone-Specific Alkaline Phosphatase and Deoxyipyridinoline-Creatinine Ratio



turnover by approximately 50%, compared with no change in the placebo group. Risedronate produced a more positive bone balance at the level of the remodeling unit, while the change in the placebo group was negative (median change, +4.0 vs -4.6 μm). Cortical thickness increased slightly from baseline with risedronate treatment compared with a negative trend in the

placebo group (median percentage change, risedronate, +20%; placebo, -11%). There was an increase in median cortical porosity in both groups (risedronate, 17%; placebo, 8%), likely due to the prolongation of the remodeling period. Cortical thickness and porosity data indicate that bone structure was preserved by risedronate treatment.

Table 3. Summary of Adverse Events by Study Group*

| | Placebo (n = 815) | Risedronate, 5 mg (n = 813) |
|---|----------------------|--------------------------------|
| Any clinical event | 774 (95) | 785 (97) |
| Drug-related adverse event | 236 (29) | 273 (34) |
| Serious adverse event† | 219 (27) | 237 (29) |
| Withdrawals for adverse events | 136 (17) | 138 (17) |
| Any upper gastrointestinal tract adverse event | 219 (27) | 245 (30) |
| Moderate-to-severe upper gastrointestinal tract event | 102 (13) | 106 (13) |
| Dyspepsia | 92 (11) | 105 (13) |
| Abdominal pain | 97 (12) | 103 (13) |
| Gastritis | 23 (3) | 31 (4) |
| Esophagitis | 13 (2) | 11 (1) |
| Duodenitis | 2 (0.2) | 9 (1) |

*Includes all subjects who were randomized and received study drug. All data are reported as number (percentage).
 †Serious adverse events were those events that were life-threatening, fatal, seriously disabling, or required hospitalization. Data are not presented for the patients in the 2.5-mg risedronate group because they experienced lower exposure of shorter duration.

COMMENT

This trial demonstrates the efficacy of risedronate in the treatment of women with established postmenopausal osteoporosis. Daily oral risedronate therapy decreased the incidence of both vertebral and nonvertebral fractures and increased BMD at clinically important skeletal sites. The primary mechanism of action of risedronate is suppression of bone turnover; this action was reflected in moderate decreases in the biochemical and histomorphometric indices of turnover.

Prevention of fractures is the primary goal of osteoporosis treatment. In this study, risedronate therapy decreased the incidence of new vertebral fractures in postmenopausal women with a history of vertebral fracture. The onset of the fracture effect was rapid, with significant decreases in new vertebral fracture incidence observed within the first year. Some other osteoporosis studies have used a vertebral height loss of 20% as the criterion for vertebral fracture,^{9,10} as opposed to the 15% definition we used. However, in a retrospective analysis, we applied a 20% fracture criterion and obtained consistent results (data not shown). Among patients who withdrew from the study, a higher proportion of placebo-treated subjects had experienced incident vertebral fractures compared with subjects in the 5-mg risedronate group. This difference may have reduced the apparent treatment effect.

The reduction in nonvertebral fractures at skeletal sites of clinical interest indicates a beneficial effect of risedronate treatment on the peripheral skeleton. This finding is important, given the significant pain and disability associated with nonvertebral fractures in osteoporotic patients. Whereas subjects receiving risedronate experienced increases in or preservation of BMD at all sites, the placebo-treated subjects, who received a high level of calcium supplementation (1000 mg/d) and cholecalciferol, if needed, showed significant losses from baseline at the femoral neck, trochanter, and midshaft radius. These BMD findings are consistent with the observed beneficial effect of risedronate treatment on nonvertebral fracture incidence and indicate that recommended levels of calcium and cholecalciferol alone are insufficient in the treatment of this patient population.

The proportion of subjects discontinuing study participation was high, but not higher than we had anticipated in the sample size calculation and not remarkably higher than that seen in other recent osteoporosis trials.²⁷⁻²⁹ Factors that might have contributed to a high withdrawal rate include the duration of the study, the age of the subjects, and the conduct of the study at a large number of study centers. There were no evident differences between the treatment groups in the proportion of

subjects discontinuing treatment or in the reasons for withdrawal. As planned, the study retained sufficient power to determine the efficacy of risedronate in preventing vertebral fractures.

A number of antiresorptive agents are reported to have antifracture efficacy in the treatment of women with postmenopausal osteoporosis. Comparisons of different agents are of much clinical interest; however, any comparison of data between studies must be viewed cautiously, due to differences in study designs and patient populations. The 2 most studied osteoporosis therapies are alendronate and risedronate. While there are differences in the magnitude of changes in BMD and biochemical markers of bone turnover observed with these 2 agents, the magnitude of the reduction in vertebral and nonvertebral fracture risk appears to be similar. This observation suggests that other effects of treatment, such as the reduction in bone turnover or changes in bone quality, may be important in the preservation of vertebral integrity.

Risedronate treatment was well tolerated in this study, with an overall safety profile similar to placebo. Upper gastrointestinal tract safety is of particular interest because of adverse effects noted during clinical use with the bisphosphonates alendronate and pamidronate.^{14,15,30,31} Although some studies of bisphosphonates have excluded subjects with specific gastrointestinal disorders,^{9,10,12} our study did not; approximately 35% of the subjects in this trial had a history of or ongoing gastrointestinal disorders at study entry. It is reassuring that the gastrointestinal safety profile of risedronate in this trial was good despite the inclusion of these subjects. Investigators were also provided with the opportunity to obtain endoscopies at their discretion in any patient with gastrointestinal complaints; these findings further support the gastrointestinal safety of risedronate. Bone safety was established by examination of the largest number of paired biopsy specimens yet reported for any osteoporosis therapy.

We conclude that oral risedronate therapy is well tolerated and produces a rapid and clinically important reduction in the risk of bone fracture in women with established postmenopausal osteoporosis. Significant reductions in the incidence of new vertebral fractures were observed in the first year of treatment, while a similar decrease in nonvertebral fractures was seen after 3 years. Risedronate is an effective and well-tolerated therapy for the treatment of postmenopausal osteoporosis.

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A contemporary poet has characterized this sense of the personality of art and of the impersonality of science in these words—"Art is myself; science is ourselves."

—Claude Bernard (1813-1878)