Alendronate Prevents Loss of Bone Density Associated With Discontinuation of Hormone Replacement Therapy

A Randomized Controlled Trial

Brynne H. Ascott-Evans, MD; Nuria Guañabens, MD; Seppo Kivinen, MD, PhD; Bronwyn G. A. Stuckey, MD; Clelia H. Magaril, MD; Kristel Vandormael, MSc; Beate Stych, MD; Mary E. Melton, MD

Background: Many women using hormone replacement therapy (HRT) will discontinue HRT and lose its bone-protective effect. Methods to preserve bone density in these women need to be explored. This multicenter, international, randomized, blinded, 12-month study was conducted to assess the effect of alendronate sodium on bone density in women who had recently discontinued HRT.

Methods: The 144 postmenopausal women included in the study were diagnosed as having low bone mineral density (BMD) and had recently discontinued HRT. They were randomized to receive either a daily dose of 10 mg of alendronate sodium or matching placebo. The main outcome measures were spine, hip, and total body BMD; biochemical markers of bone turnover; and tolerability.

Results: Alendronate treatment was associated with a 2.3% mean increase (95% confidence interval [CI], 1.7%-3.0%) in spine BMD compared with a mean loss of 3.2% (95% CI, −4.6% to −1.7%) in patients receiving placebo, for a difference of 5.5% (95% CI, 4.2%-6.8%) between alendronate and placebo. Greater hip and total body BMD preservation was also observed with alendronate use. Bone turnover decreased significantly with alendronate (bone-specific alkaline phosphatase levels decreased by 20% and urinary N-telopeptide/creatinine ratio by 47%), but increased in the placebo group (by 18% and 36%, respectively). Alendronate was well tolerated, with no increase in adverse events compared with placebo.

Conclusions: A high rate of bone loss was observed in the first 12 to 15 months after discontinuation of HRT in postmenopausal women with low BMD. Treatment with alendronate increased or maintained both spine and hip BMD and prevented the increase in bone resorption seen with withdrawal of HRT in this population.

Arch Intern Med. 2003;163:789-794
bral fracture, including hip fracture. Whether the bone loss occurring after HRT withdrawal can be alleviated by alendronate is unknown.

The purpose of this study was to evaluate the efficacy and safety of alendronate in postmenopausal women with low bone density who have recently discontinued HRT. The primary hypotheses were that treatment with alendronate sodium would be found to significantly increase the bone mineral density (BMD) of the lumbar spine compared with placebo treatment, and would be safe and well tolerated. In addition, effects of alendronate on hip and total body BMD, and on biochemical markers of bone turnover, were evaluated and compared with the corresponding effects of recent HRT discontinuation in the women receiving placebo.

METHODS

Study patients were recruited at 18 centers in 9 countries. Women were eligible for enrollment if they were younger than 80 years, had been postmenopausal for at least 3 years, had used HRT for at least 1 year, and had discontinued HRT within the 3 months preceding their joining the study. In addition, patients had to have a low bone density defined as a lumbar spine T score between −3.5 and −1.5 (approximately 1.5 to 3.5 SDs below the mean BMD for healthy young women). Patients were excluded from participation if they had a history of other metabolic bone disease or osteoporotic fracture, or if they had recently received bisphosphonate or other treatments (such as glucocorticoid therapy) known to affect bone metabolism. An ethics committee review was obtained for each participating study site. Informed consent was received from all patients before any study procedures were performed.

Patients were randomly assigned to a double-blind, 12-month daily treatment of either a 10-mg tablet of alendronate sodium (Fosamax; Merck & Co, Inc, Whitehouse Station, NJ) or a matching placebo tablet in a 2:1 ratio using a computer-generated random allocation schedule. The randomization was stratified based on the time elapsed since HRT discontinuation (≤30 days, and 31 days to 3 months). All investigators, study personnel, patients, and other research personnel were blinded to the treatment assignment. Unblinding of the data occurred only after all patients had completed the study and after all data had been entered into the database and checked for accuracy. Patients were instructed to take the study tablet with 125 mL of water at least 30 minutes before the first food or beverage of the day, and to remain upright for at least 30 minutes. Any other medications were delayed for at least 30 minutes. Calcium supplementation (500 mg/d) was provided for all patients.

Bone mineral density was measured at baseline and at 3, 6, and 12 months by dual-energy x-ray absorptiometry (Hologic, Inc, Waltham, Mass, or Lunar Corp, Madison, Wis) at the lumbar spine (anteroposterior) and hip. Total body BMD was measured at baseline and 12 months in a subset of patients. A BMD quality assurance center was used for central analysis of the BMD data (Medical Data Management, Waltham, Mass). To maintain blinding, no interpretation of scans was permitted at the study sites.

Serum bone-specific alkaline phosphatase (BSAP) (Ostase; Beckman-Coulter, Inc, San Diego, Calif) and urinary N-telopeptide of type I collagen corrected for creatinine (NTx) (Osteomark; Ostex International, Inc, Seattle, Wash) were used to evaluate bone formation and bone resorption, respectively. Samples were collected at baseline and at 3 and 12 months. The analysis of biochemical markers was conducted at the completion of the study by a central laboratory (Medical Research Laboratory, Highland Heights, Ky).

The safety and tolerability of alendronate were evaluated using the incidence of adverse experiences, the results of physical examinations, and analysis of routine laboratory tests. Adverse experiences were recorded by study-site personnel at each visit using nonleading questions.

The primary objectives were to evaluate the effect of alendronate relative to placebo on changes in lumbar spine BMD at 1 year, and the treatment’s safety and tolerability as assessed by adverse experience reporting. Secondary objectives included the effect of alendronate relative to placebo at 1 year on proximal femur (femoral neck and trochanter) and total body BMD, and the effect on biochemical markers of bone turnover. A sample size of 99 patients (66 in the alendronate group and 33 in the placebo group) was found necessary to detect a difference between groups of 3.5% in mean change from baseline in lumbar spine BMD at 1 year with 95% power, assuming an SD of 4.5% and using a 2-tailed test at a 5% significance level. Assuming a dropout rate of up to 40% in this patient population, additional patients were enrolled to ensure that at least 99 of them completed the study. Analyses of efficacy were based on the intention-to-treat principle; all women who had a baseline measurement and at least one measurement after randomization were included in the analyses, irrespective of protocol violations. For the primary analysis of BMD efficacy variables, missing values were assigned by carrying forward the corresponding values of the last follow-up. Treatment differences were assessed using analysis of variance on percent changes from baseline. The main analysis of variance model included factors for treatment group, country, and stratum. A per protocol analysis and a completers analysis, in which data were not carried forward, were also performed for lumbar spine BMD. For biochemical markers of bone turnover, log-transformed percentages of baseline values were used. All treatment comparisons were 2-sided and statistical significance was defined as P ≤.05. Proportions of patients with an adverse experience and with a change in laboratory variables exceeding predefined limits were compared between groups using the Fisher exact test. Statistical analyses were conducted using SAS 6.12 software (SAS Institute, Cary, NC).

RESULTS

Of the 144 patients enrolled in the study, 95 were randomized to receive alendronate and 49 to receive placebo. The characteristics of the groups were similar at baseline (Table). A total of 119 patients (83%) completed the study (87% in the alendronate group and 74% in the placebo group). In the 6 months preceding their joining the study, the most commonly used HRT regimens were estradiol (70%) and conjugated estrogens (27%). During the course of the study, 20% of the patients used a nonsteroidal anti-inflammatory agent. Thirty percent of the patients reported a prior history of gastrointestinal disease.

Treatment with alendronate significantly increased lumbar spine BMD when compared with placebo. There was a 5.5% difference between the groups at 12 months (95% confidence interval [CI], 4.2%-6.8%; P < .001) (Figure 1); and after 12 months, alendronate treatment was associated with a mean lumbar spine BMD increase of 2.3% (95% CI, 1.7%-3.0%) vs baseline, as compared with a mean loss of 3.2% (95% CI, −4.6% to −1.7%) vs baseline in the placebo group. The per protocol and completers analyses gave similar results. Also,
results were similar in those with a baseline lumbar spine BMD T score equal to or less than −2.0 or greater than −2.0. Among patients taking placebo, 41.5% had a lumbar spine BMD decrease of 5% or greater; of those taking alendronate, none experienced a loss of such magnitude whereas 49.4% gained more than 2%.

Significant BMD increases in the treatment group were also noted for the femoral neck, hip trochanter, and the total body compared with the placebo group (Figure 1). At the femoral neck, BMD was maintained in the group treated with alendronate at 12 months (change vs baseline, 0.2%; 95% CI, −0.6% to 1.0%) whereas a significant decline in BMD was seen in the group taking placebo (change vs baseline, −1.4%; 95% CI, −2.3% to −0.4%). At the hip trochanter, BMD increased in the group treated with alendronate (change vs baseline, 2.5%; 95% CI, 1.6%-3.5%) but was unchanged in the group receiving placebo (change vs baseline, 0.2%; 95% CI, −1.4% to 1.8%). An increase in BMD was seen for the total body in the group treated with alendronate (change vs baseline,1.0%; 95% CI, 0.4%-1.6%) and a nonsignificant decrease of 0.7% was seen in the group given placebo (95% CI, −1.6% to 0.1%). For all BMD sites, the observed treatment effects were consistent for patients who discontinued HRT within 30 days of randomization and for patients who discontinued HRT between 30 days and 3 months before randomization.

Treatment with alendronate significantly decreased both BSAP and NTx compared with placebo (P<.001 for both parameters) (Figure 2). At 12 months, mean NTx level had fallen by 46.7% vs baseline (95% CI, −55.6% to −36.2%) in patients treated with alendronate, whereas it had risen by 35.7% (95% CI, 6.7%-72.4%) with placebo. At 12 months, a 19.6% decrease in BSAP vs baseline (95% CI, −26.7% to −11.8%) was observed in patients treated with alendronate compared with an increase of 17.9% (95% CI, 1.8%-36.6%) in patients receiving placebo.

The tolerability of alendronate was comparable to that of placebo. Overall, a clinical adverse experience was reported by 60 women receiving alendronate (60%) and 30 women receiving placebo (61%). The percentages of women reporting a clinical adverse experience that was considered possibly, probably, or definitely related to the study drug were also similar in the 2

### Baseline Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Alendronate Sodium Group</th>
<th>Placebo Group</th>
<th>Total</th>
</tr>
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<tbody>
<tr>
<td>Age, y</td>
<td>57.3 (6.6)</td>
<td>57.3 (6.7)</td>
<td>57.3 (6.6)</td>
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<tr>
<td>&lt; 65, %</td>
<td>84.2</td>
<td>85.7</td>
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<td>Race, %</td>
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</tr>
<tr>
<td>White</td>
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<td>89.8</td>
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</tr>
<tr>
<td>Other</td>
<td>7.4</td>
<td>10.2</td>
<td>8.3</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>24.8 (3.3)</td>
<td>24.9 (3.7)</td>
<td>24.8 (3.4)</td>
</tr>
<tr>
<td>Years postmenopausal</td>
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<td>11.6 (7.2)</td>
<td>11.5 (7.3)</td>
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<tr>
<td>Lumbar spine BMD T score</td>
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<td>−2.22 (0.78)</td>
<td>−2.27 (0.65)</td>
</tr>
<tr>
<td>Bone-specific alkaline</td>
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<td>10.20 (2.69)</td>
<td>10.19 (3.29)</td>
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<td>phosphatase, ng/mL</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Urinary N-telopeptide/creatinine ratio, pmol BCE/µmol</td>
<td>41.03 (24.25)</td>
<td>41.49 (27.98)</td>
<td>41.19 (25.45)</td>
</tr>
</tbody>
</table>

*Data are given as mean (SD) unless otherwise noted. BMI indicates body mass index; BMD, bone mineral density; and BCE, bone collagen equivalents.
fractures were reported during the study. In this patient population (postmenopausal women with T scores ≤ −2.0) who had not been receiving estrogen, a daily dose of 10 mg of alendronate sodium or placebo for 1 year resulted in mean lumbar spine bone density increases of 5% in the treatment group and 0.1% in the placebo group at 12 months. The absolute difference between the alendronate and placebo groups in that study was very similar to the 5.5% difference seen in our study.

Estrogen withdrawal, whether due to menopause or to discontinuation of HRT, has been shown to be associated with an increase in the release of bone-resorbing cytokines such as interleukin 1 and tumor necrosis factor. Therefore, increased bone resorption is thought to be the mechanism responsible for the accelerated bone loss observed with estrogen withdrawal. It follows that administration of an antiresorptive agent such as alendronate would be expected to decrease this bone loss, which this study demonstrated. A prior study showed that administration of antiestrogens (tamoxifen and toremifene) did not prevent spine bone loss upon HRT withdrawal, but it reported that the bisphosphonate clodronate seemed to retard bone loss.

The mean loss of 3.2% in lumbar spine bone density observed over 12 months after discontinuation of HRT in the present study is similar to previous observations. The results of a 1-year extension to a 2-year randomized controlled trial evaluating estrogen and alendronate therapy further corroborate this observation. Patients who were switched from estrogen therapy to placebo during the third year experienced a mean loss of 4.2% in lumbar spine bone density. In contrast, after discontinuation of alendronate in clinical trials, the bone density gained during therapy was maintained and the reductions in markers of bone turnover were sustained for at least 6 to 24 months.

Although both alendronate and estrogen are antiresorptive agents, additional benefit has now been shown from sequential use, as demonstrated in this study, and combination use. A recent study has shown no loss of lumbar spine BMD upon discontinuation of alendronate and estrogen when both had been used concomitantly over the 2 previous years, suggesting a prolonged protective effect of the combined use of alendronate and HRT. Concomitant therapy with these two antiresorptive agents for postmenopausal women with low BMD has the additional benefit of greater increases in bone density than those seen with HRT alone. It has also been shown that the addition of alendronate therapy to HRT in women who still have low bone density despite at least a year of HRT substantially increased both spine and hip BMD. Given these additional benefits of alendronate use in women who are either receiving HRT or have discontinued it suggests that use of both alendronate and estrogen has an additive benefit on bone. Unfortunately these studies have not been large enough to assess the effect of combination or sequential therapy on fracture risk.

In this study, the decrease in bone resorption with alendronate was greater than might have been expected in a patient population who had recently used HRT. The

Figure 2. Mean percent change from baseline and 95% confidence intervals (CIs) for serum bone-specific alkaline phosphatase (A) and urinary N-telopeptide corrected for creatinine (B) during 12 months of therapy with alendronate (12%) (P<.001); none was considered serious. No gastrointestinal tract events were reported by 15 patients treated with alendronate (16%) and by 6 receiving placebo (12%) (P=.63); none was considered serious. No fractures were reported during the study.

We found a substantial decrease, of approximately 3%, in the bone density of the lumbar spine over a 12-month period in patients having recently discontinued HRT. Nearly 42% of them sustained a loss of 5% or greater in the bone density of the spine. Treatment with alendronate not only prevented this loss but was also associated with a mean lumbar spine BMD gain of over 2% at 1 year. This study demonstrates the efficacy of alendronate in preventing the rapid decline in bone density occurring upon HRT withdrawal.

The relative changes in the bone density of patients treated with alendronate or receiving placebo ob-
time between HRT discontinuation and the start of treatment with alendronate was up to 3 months. This may have allowed increases in bone resorption and resulted in higher absolute values of bone turnover than if alendronate treatment had been started immediately upon discontinuation of HRT. Nevertheless, the further increases in bone resorption observed in the patients who took placebo show that the bone turnover had not yet stabilized in this group. Alendronate not only prevented further increases in bone resorption but it reduced bone resorption further despite recent HRT.

The increases in bone resorption in the placebo group were also substantial, suggesting either a return to baseline or, possibly, a rebound effect following HRT discontinuation. The suggestion that increased bone resorption is related to fracture risk makes these results a special cause for concern. Studies on the relationship of estrogen use and fracture risk have shown that the fracture prevention benefit of estrogen is not sustained upon discontinuation of estrogen. This phenomenon may be explained, at least in part, by the increase in bone resorption, the decrease in bone density, or a combination of both factors following HRT withdrawal.

The number and types of adverse events were similar in the study’s two groups. Therefore, alendronate was generally well tolerated in this patient population. Interestingly, 16% of the patients reported hot flashes during the study, and 5% left the study because of hot flashes, presumably to resume HRT. It is important to be aware that hot flashes can be a significant concern in some patients who are discontinuing HRT.

Other options for the maintenance of bone density after HRT discontinuation include a selective estrogen receptor modulator such as raloxifene. However, raloxifene use is known to increase the occurrence of hot flashes and therefore may not be well tolerated in this patient population. In addition, no data are yet available to assess whether raloxifene can maintain bone density in patients discontinuing HRT; and there are no data on the effect of other available agents, such as other bisphosphonates or calcitonin, in this patient population.

One of the strengths of this study is that we were able to enroll patients within 3 months of HRT discontinuation. This allowed us to collect data on the early effects of HRT withdrawal on bone density. Other strengths of the study are that it was multicenter, randomized, blinded, and placebo controlled.

Although the increases in bone density and decreases in bone turnover seen in patients treated with alendronate have been associated with a reduction in fracture risk, this study was not large enough to determine the fracture risk reduction. Another limitation of this study is that the patients had only moderate low bone density and no prior osteoporotic fracture. Because similar increases in bone density regardless of baseline BMD and history of vertebral fracture have been seen with alendronate use, it would be expected that a population with more severe osteoporosis or with prior fractures would have similar results. The dropout rate of 17%, although higher than in most other studies of alendronate, was less than was anticipated in the study population and its effect on the lumbar spine BMD analyses was minimal. This was confirmed by the finding of similar results of the per protocol and completers analyses with those of the intention-to-treat analysis. Also, because the duration of this study was limited to 12 months, the effects of HRT discontinuation and the addition of alendronate over a longer period cannot be ascertained from this study. The loss of lumbar spine and femoral neck BMD in the placebo group continued in a nearly linear fashion through 12 months, with no evidence of slowing. This suggested that bone density would continue to decrease beyond 12 months following HRT withdrawal.

In conclusion, this study has documented significant bone loss in the first 12 to 15 months after HRT discontinuation in postmenopausal women with low bone density. Alendronate treatment increased or maintained bone density and also prevented the increase in bone resorption observed upon HRT discontinuation. The use of alendronate should be considered whenever HRT is discontinued in a postmenopausal woman in whom osteoporosis is a concern.

Accepted for publication June 24, 2002.

This study was funded by Merck & Co, Inc, which markets alendronate.

This study was presented in abstract form at the 26th European Symposium on Calcified Tissues, Maastricht, the Netherlands, May 8 and 10, 1999.

We acknowledge Keavy Gaines for the administrative coordination of this study and William Malbecq for statistical review and preparation of graphs.

The following lead investigators participated in this study: Argentina: C. Magaril; Australia: B. Stuckey; Austria: J. Huber; Brazil: N. Melo; Finland: S. Kivinen, E. Hirvon; Germany: V. Furstenhofer, K. Dittmar, H. Stracke, G. Steuer; New Zealand: R. Toomath; South Africa: B. Ascott-Evans; J. Adno; Spain: N. Guanabal, J. Quesada Gomez, J. Gonzalez-Macias, M. Romera, A. Cabeiro I Roua.

Corresponding author: Brynne H. Ascott-Evans, MD, Metabolic Bone Unit, University of Stellenbosch Medical School and Tygerberg Hospital, Department of Endocrinology, Ward A10, Tygerberg 7505, South Africa.

Reprints: Mary E. Melton, MD, Merck & Co, Inc, 1 Merck Dr, WS 3CD-45, Whitehouse Station, NJ 08889.

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