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Skeletal Benefits of Alendronate: 7-Year Treatment of Postmenopausal Osteoporotic Women*

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ABSTRACT

We report here the second 2-yr extension of a clinical trial among postmenopausal women; 235 women continued blinded treatment with 5 or 10 mg alendronate daily, and 115 women who had been treated with alendronate for 5 yr were switched to blinded placebo. Continuous treatment with alendronate (10 mg daily) for 7 yr increased lumbar spine bone mineral density (BMD) by 11.4% compared to baseline. After the initial 18 months, each additional year of treatment through yr 7 increased spine BMD by 0.8% for the 10-mg dose and 0.6% for the 5-mg dose, with significant increases during yr 6–7. Previously reported increases in BMD at other skeletal sites and decreases in biochemical markers of bone turnover remained stable during yr 6–7. Among women previously taking alendronate for 5 yr who were switched to placebo, there was no significant decline in BMD at the spine or hip, whereas small, but significant, decreases in BMD at the forearm and total body and small increases in biochemical markers were observed. The safety and tolerability profiles were similar to those of placebo. This is the largest published long-term study of antiresorptive therapy. Our findings indicate that long-term alendronate treatment is well tolerated and effective for 7 yr. Increases in spinal BMD continue for at least 7 yr, and other skeletal benefits are maintained. Discontinuation does not lead to accelerated bone loss, but continuous treatment yields better skeletal benefits than shorter treatment. (*J Clin Endocrinol Metab* **85:** 3109–3115, 2000)

FRACTURES RELATED to osteoporosis represent an enormous health problem among the elderly, especially among women (1–6). About the time of menopause, bone turnover increases and remains elevated (7). Combined with an imbalance favoring bone resorption over formation, this leads to decreases in the amount (mass) and connectivity (microarchitecture) of bone tissue, thereby reducing bone strength. Bone mineral density (BMD) is an important indicator of skeletal health, reflecting both the amount of bone tissue and the degree of mineralization. BMD decreases and fracture risk increases progressively over time, especially after menopause (4). Inhibitors of bone resorption can treat this bone loss and reduce fracture risk (8).

Alendronate is a potent inhibitor of bone resorption. It increases BMD, reduces bone turnover (as measured by biochemical markers of bone turnover and bone histomorphometry) to premenopausal levels, and substantially reduces the incidence of vertebral and nonvertebral fractures among postmenopausal women (8–13). In patients with osteoporosis the incidence of new hip fractures is reduced by 63% within 18 months, the incidence of symptomatic new vertebral fractures is reduced by 59% within 12 months, and the incidence of multiple vertebral fractures is reduced by 90% (11, 14, 15). Alendronate has been studied in more than 17,000 participants in clinical trials and has been prescribed to more than 3 million patients worldwide as FOSAMAX (Merck & Co., Inc., Whitehouse Station, NJ).

Long-term treatment with antiresorptive therapy is probably needed by many patients, as current drugs for treatment of osteoporosis do not fully restore bone mass to healthy young adult levels. Therefore, it is important to evaluate the long-term safety and efficacy of antiresorptive agents. The initial placebo-controlled phase III studies of alendronate were designed to end after 3 yr (9). Although information from long-term follow-up to evaluate efficacy and safety would have been useful, it was no longer considered ethical to continue a placebo-controlled trial after the beneficial effects of alendronate to reduce fracture risk had been demonstrated. Thus, a 2-yr open label extension was conducted to increase the follow-up to 5 yr, with all women receiving alendronate (16). Treatment of postmenopausal osteoporotic women with alendronate (10 mg/day) for 5 yr produced progressive increases in BMD in the spine and hip and prevented bone loss in the forearm. At the end of 5 yr, BMD had increased at the lumbar spine, femoral neck, and trochanter relative to baseline by 9.4%, 4.8%, and 9.1%, respectively, among women taking continuous alendronate (10 mg/day) (16). Biochemical markers of bone turnover were decreased into the normal premenopausal range within 6 months and remained stable throughout the 5 yr among women taking alendronate. Safety and tolerability were similar between the 5- and 10-mg alendronate doses and were comparable to those for placebo during the initial 3 yr of the trial.

The primary objective of the current study was to examine the efficacy (as measured by changes in BMD and biochem-

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ical markers), safety, and tolerability of an additional 2 yr of alendronate treatment in these same patients, yielding a total of 7 yr of continuous alendronate treatment at doses of both 5 and 10 mg daily. A secondary objective was to examine skeletal changes occurring over 2 yr of alendronate discontinuation after 5 yr of continuous use.

Subjects and Methods

Study design and participants

Two nearly identical randomized, double blind, placebo-controlled phase III clinical trials of 3-yr duration were conducted in the United States (18 sites) and other countries (19 sites in 15 countries) to evaluate the safety and efficacy of daily oral alendronate (9). These studies enrolled a total of 994 postmenopausal women with osteoporosis, as defined by spine BMD at least 2.5 SD below the mean for young healthy women (corresponding to $\leq$0.80 g/cm^2 on Hologic, Inc., model 1000 densitometers, Waltham, MA). The women were randomized to receive alendronate (5, 10, or 20 mg daily), or placebo of identical appearance (Fig. 1). The 20-mg dose was changed to 5 mg for yr 3, based on results from a separate study indicating that 20 mg was more than necessary to obtain maximal increases in BMD.

Of the 824 women who completed the original 3-yr study, 727 women consented to continue participation in a double blind 2-yr extension (yr 4 and 5), and 61 women chose an open label treatment option in which they knowingly received alendronate (10 mg/day) (16). The placebo group was switched to alendronate (10 mg daily) for yr 4–5, because it was not considered ethical to continue using placebo in view of data demonstrating that alendronate decreased the rate of vertebral fractures (9). The women who were originally randomized to alendronate continued the same dose as that in yr 3, maintaining the double blind during the 2-yr extension. Thus, all women knew they were receiving alendronate in yr 4–5, but did not know the dose (except the original placebo group, who knew they were receiving 10 mg alendronate in yr 4–5).

A second 2-yr extension, from the end of yr 5 to the end of yr 7, maintained the double blind treatment assignments from yr 3 for women who were originally randomized to alendronate (5 or 10 mg). Women who received alendronate (20 mg initially, then 5 mg in yr 3–5) received placebo (designated 20/5/PBO) during this second extension (Fig. 1). Women from the original placebo group, who represented 40% of the total, were ineligible for the second extension. The current report describes data for the women who entered the second 2-yr extension for yr 6 and 7 (n = 350, representing 59% of women originally randomized to alendronate).

Participants were instructed to take the study medication each morning with 6–8 oz water at least 0.5 h before consuming any food or drink (except water). All patients received 500 mg/day calcium supplementation (as carbonate, OsCal; SmithKline Beecham, Pittsburgh, PA), and were instructed to take it with a meal, separate from the morning dose of alendronate. Participants taking vitamin D supplements were not excluded, and vitamin D supplements were not provided.

The primary efficacy end point in these studies was change in lumbar spine BMD. The secondary end point was BMD changes at the proximal femur hip (femoral neck, trochanter, and Ward's triangle). Additional secondary end points included changes in forearm and total body BMD, and changes in biochemical markers of bone resorption [urinary N-telopeptides of type I collagen corrected for creatinine (NTX)] and bone formation [serum bone-specific alkaline phosphatase (BSAP)].

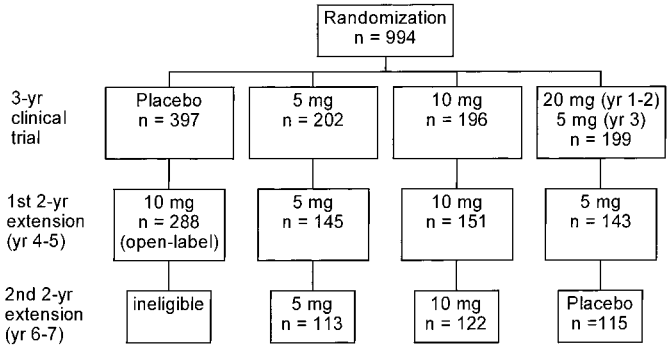

FIG. 1. Treatment group assignments and derivation of the participants. All treatment assignments were blinded, except the initial (yr 1–3) placebo group knew they were receiving 10 mg alendronate in yr 4–5.

Measurements

BMD was measured by dual energy x-ray absorptiometry using Hologic, Inc., QDR, Lunar Corp. DPX-L (Madison, WI), or Norland XR-26 (Fort Atkinson, WI) densitometers, using prespecified standard operating procedures. All BMD scans were reviewed at the study site and by a quality assurance center (Hologic, Inc., MDM/Synarc,), while maintaining the double blind. Measurements of a BMD calibration phantom that was circulated to all sites were used to monitor calibration of dual energy x-ray absorptiometry instruments during the study, and each site measured a spine BMD phantom at routine intervals; no corrections for changes in calibration during the study were necessary.

Serum and urinary biochemical markers of bone turnover were measured at a central laboratory (Medical Research Laboratories, Cincinnati, OH). Urinary NTX, a marker of bone resorption, was measured using Osteomark kits (Ostex International, Inc., Seattle, WA). Serum BSAP, a marker of bone formation, was measured using Ostase kits (Beckman Coulter, Inc.-Coulter, San Diego, CA). Stature was measured annually to the nearest millimeter using a Harpenden stadiometer (Seritex, Inc., Carlstadt, NJ), because decreases in height are a surrogate measure of new vertebral fractures. The value for height was the average of three to five measurements obtained at each visit.

Analyses

The data from the two multicenter studies (U.S. and other countries) were pooled, as the designs and subject characteristics of the two studies were nearly identical. Study and treatment center interactions were examined in analyses where appropriate. Summary statistics and analyses of change in efficacy and safety parameters during this extension study are limited to the 350 women who were enrolled into the second 2-yr extension study (yr 6–7). Therefore, changes during the first 3 and 5 yr of treatment reported here are similar, but not identical, to those previously reported for all patients initially enrolled (9, 16).

Percent changes from month 60 and baseline were used to assess the effect of treatment on BMD, stature, and biochemical markers at month 84. The intention to treat principle was used in analyses of BMD and stature; data from the last point of evaluation were carried forward in patients who withdrew from the second extension study before study completion or for whom follow-up measurements were inadequate. Thus, analyses included all patients who had at least one measurement after month 60. Due to the changes in treatments and medication doses in some groups, biochemical marker analyses were performed per protocol, with no data carried forward from subjects who discontinued before the end of the study, as these markers were included to evaluate the clinical pharmacology of alendronate and may not be adequate surrogates for clinical efficacy. A natural log transformation was used to normalize the distribution of the changes in biochemical parameters (fraction of value at month 0) for analysis.

ANOVA was used to examine treatment effect. Within each treatment group, changes were tested using paired *t* tests. A least squares mean change and its confidence interval (CI) was computed for all treatment groups, adjusted for study and clinical center.

Safety and tolerability were evaluated based on original treatment group randomization. All clinical and laboratory adverse experiences were reviewed, including those that were considered serious or drug related (*i.e.* rated by the investigator as possibly, probably, or definitely drug related) or that resulted in patient withdrawal from the study. Fisher's exact test was used to compare proportions of patients with clinical adverse experiences between 5- and 10-mg treatment groups. Fisher's test was not used for comparisons to placebo because the 20/5/PBO group did not take placebo continuously for all 7 yr, and prior exposure to alendronate may have influenced outcomes such as fracture, thereby complicating interpretation. Safety was also assessed by analyzing weight, blood pressure, and pulse rate for within- and between-group differences in changes from baseline and by analyzing the pro-

portions of patients with laboratory parameters exceeding predefined limits (or changes) in laboratory variables. All reported symptomatic nonvertebral and vertebral fractures were considered adverse experiences, with no attempt to exclude those fractures related to excessive trauma. All fractures were confirmed by radiographs.

Results

Baseline characteristics

At baseline (month 0), the 350 women in the current extension study (yr 6–7) had a mean age of 63 yr and were 16 yr postmenopause. Their mean spinal BMD was 0.71 (SD = 0.08) g/cm^2 (measured on Hologic, Inc., and Norland densitometers), and 21% had existing vertebral fractures at baseline. The geometric mean urinary NTX/creatinine was 87.5 nmol Bone Collagen Equivalents/mmol creatinine, and the mean BSAP was 18.1 ng/mL. Mean dietary calcium intake was 734 mg/day, and mean body mass index was 24 kg/m^2. In general, the baseline characteristics of the patients who did not enter the current extension study were similar to those of the patients who entered the extension (data not shown). Among those who entered the current extension, the treatment groups were generally comparable to each other at baseline (month 0), except that the prevalence of vertebral fracture was 23.4%, 14.8%, and 26.4% in the 5 mg, 10 mg, and 20/5/PBO groups, respectively. Additional details of baseline patient characteristics were provided in a previous report for all patients enrolled (9).

Effect of continued alendronate

Seven years of treatment resulted in a total lumbar spine BMD increase of 11.4% for the 10 mg group and 8.2% for the 5 mg group compared to baseline (month 0). Lumbar spine BMD increased significantly by 1.6% in the 10-mg group and 1.5% in the 5-mg group treated with alendronate during yr 6–7, relative to that at the 60 month point (Fig. 2 and Table 1). The increase in BMD appeared to be linear after 18 months (based on visual inspection) for the continuous administration groups, as shown in Fig. 2. Linear regression was used to estimate the slope of mean change in BMD *vs.* time between 18 and 84 months. The slope indicates that each additional year of treatment increases spine BMD by 0.83% (SE = 0.07) for the 10-mg dose and 0.58% (0.05) for the 5-mg dose. The proportion of women whose spine BMD increased relative to that at month 0 was 97% for the 10 mg group, and 88% for the 5 mg group.

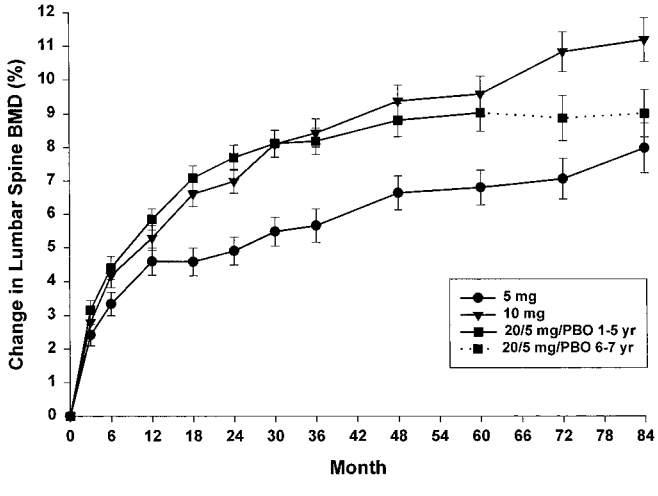

FIG. 2. Mean percent change (SE) in lumbar spine BMD, by treatment group. Analysis followed the intention to treat principle.

The increases in hip BMD during the first year of treatment were maintained through 7 yr and did not appear to either increase or decrease after the 36 month point, except for a small increase ($P < 0.05$) in trochanter BMD in the 10 mg group during yr 4 and 5 (16). The changes in femoral neck and trochanter BMD from month 60 to month 84 were not significantly different from zero for either dose (Figs. 3 and 4 and Table 1). Overall, larger BMD increases were observed at the hip trochanter than the femoral neck. At the end of 7 yr, trochanter BMD had increased 9.5% for the 10 mg group and 5.6% for the 5 mg group, compared to 4.9% and 2.6%, respectively, at the femoral neck, relative to baseline (Figs. 3 and 4 and Table 1). The increase in total body BMD and prevention of loss of forearm BMD through yr 5 were maintained, but did not change, with both alendronate groups (5 and 10 mg) over yr 6 and 7 (Table 1).

Substantial reductions in biochemical marker levels were observed within months after randomization (Figs. 5 and 6). Within 3 months, urinary NTX was reduced to approximately −75% relative to baseline in the 10 mg group and remained relatively stable in subsequent years. NTX in the 5-mg dose group was initially reduced to approximately −65%, and gradually declined further to coincide with mean NTX levels of the 10 mg group at the end of 84 months, −71.3% (95% CI, −66.8, −75.9) for 5 mg and −71.9% (−68.4, −75.5) for 10 mg. Serum BSAP was reduced to approximately −55% for the 10 mg group, with a final value of −52.3% (−48.8, −55.8) at month 84. For the 5 mg group, BSAP was reduced to approximately −40% relative to baseline within 6 months and then declined to approximately −50% after 36 months, with a final value of −44.6% (−40.9, −48.2) at month 84.

Effect of alendronate discontinuation

There were no significant changes in BMD at the spine and hip during yr 6–7 in the 20/5/PBO group (switched to placebo after 5 yr of alendronate treatment; 2 yr of 20 mg, followed by 3 yr of 5 mg), although there were small, nonsignificant declines at the hip based on visual inspection (Table 1, Figs. 3 and 4). Small, but significant, declines in BMD occurred at total body and forearm. At the end of 84 months, BMD in the 20/5/PBO group was higher than baseline by 8.9% at the spine, 6.8% at the trochanter, and 3.2% at the femoral neck (Table 1 and Figs. 2–4). These values were intermediate between the groups that had received 5 and 10 mg alendronate continuously for 7 yr, reflecting the cumulative alendronate exposure of these three groups.

Discontinuation of alendronate resulted in small increases in urinary NTX and serum BSAP in yr 6–7 compared to levels observed during treatment (Figs. 5 and 6). NTX remained stable, however, between months 72 and 84, after increasing from approximately −73% at 60 months to a final value of −57.9% (95% CI, −52.6, −63.1). Serum BSAP also remained well below baseline, increasing gradually over time from approximately −55% at month 60 to −36.7% (−32.4, −40.9) at the end of 7 yr.

TABLE 1. Percent change in BMD at the end of 84 months, by treatment group

Measurement	Change from month 60			Change from baseline		
	5 mg	10 mg	20/5 mg/PBO	5 mg	10 mg	20/5 mg/PBO
Lumbar spine BMD (%)	1.45 (0.71, 2.19)	1.60 (0.92, 2.28)	0.20 (−0.51, 0.91)	8.20 (6.74, 9.66)	11.44 (10.13, 12.75)	8.94 (7.53, 10.36)
Femoral neck BMD (%)	0.32 (−0.77, 1.41)	0.49 (−0.53, 1.51)	−0.46 (−1.54, 0.62)	2.64 (1.26, 4.02)	4.87 (3.56, 6.18)	3.15 (1.85, 4.46)
Trochanter BMD (%)	0.04 (−0.98, 1.05)	0.20 (−0.75, 1.15)	−0.47 (−1.48, 0.53)	5.60 (4.05, 7.14)	9.51 (8.04, 10.98)	6.79 (5.33, 8.26)
Total body BMD (%)	−0.29 (−0.76, 0.17)	0.35 (−0.08, 0.78)	−0.50 (−0.95, −0.04)	1.65 (0.94, 2.36)	3.13 (2.47, 3.78)	2.46 (1.76, 3.16)
Forearm BMD (%)	0.06 (−0.61, 0.72)	0.31 (−0.35, 0.97)	−0.84 (−1.53, −0.15)	−0.24 (−1.32, 0.84)	1.04 (−0.03, 2.10)	0.38 (−0.70, 1.46)

Values shown are adjusted means (95% confidence intervals in *parentheses*).

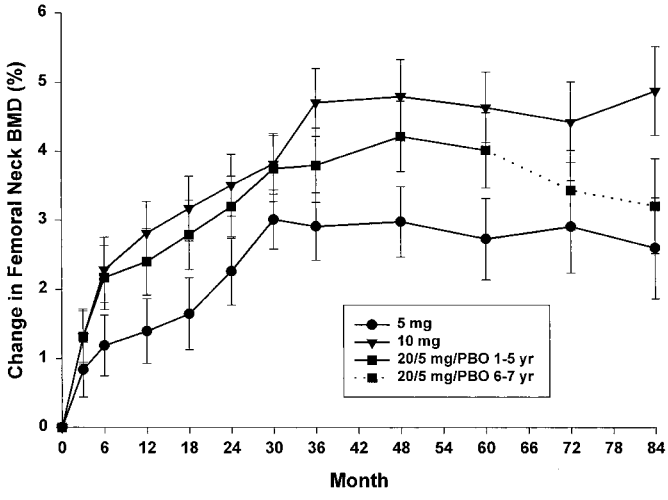

FIG. 3. Mean percent change (SE) in femoral neck BMD by treatment group. Analysis followed the intention to treat principle.

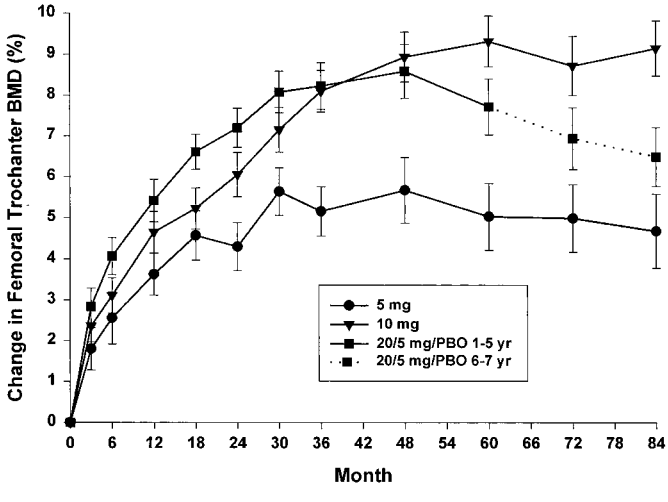

FIG. 4. Mean percent change (SE) in hip trochanter BMD, by treatment group. Analysis followed the intention to treat principle.

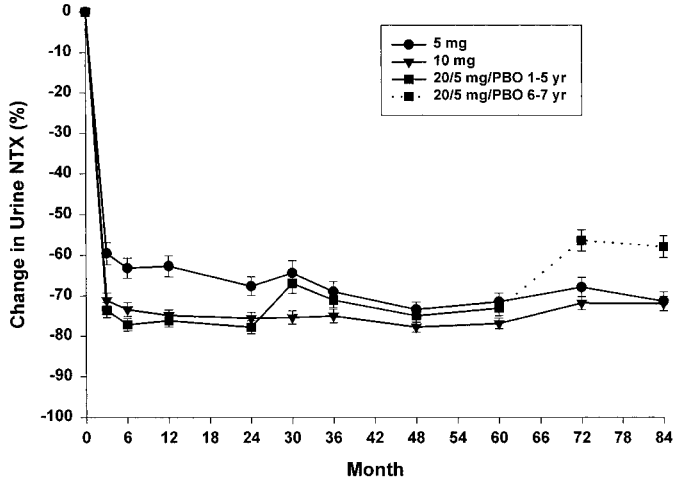

FIG. 5. Mean percent change (SE) in urinary NTX by treatment group. Analysis followed the per protocol principle.

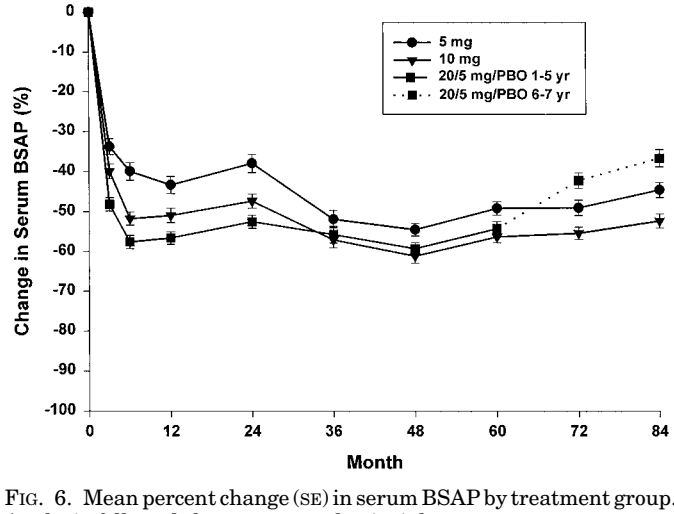

FIG. 6. Mean percent change (SE) in serum BSAP by treatment group. Analysis followed the per protocol principle.

Safety and tolerability

Alendronate (both 5 and 10 mg) was well tolerated during yr 6–7; the safety and tolerability profiles were similar to those of placebo (Table 2). In particular, the incidence of upper gastrointestinal adverse events, both overall and those considered by the investigator to be drug related (possibly, probably, or definitely), was similar to that of placebo for both the 5- and 10-mg doses (Table 3). Two patients withdrew due to upper gastrointestinal adverse events in the placebo group compared to zero and one patient, respectively, in the 5 and 10 mg groups. No patients died during yr 6–7 in any group.

TABLE 2. Overall adverse experiences (AE) by treatment group during yr 6–7

AE	Placebo (n = 115)[a]	5 mg alendronate (n = 113)	10 mg alendronate (n = 122)
No. (%) of women with any AE (≥1)	104 (90.4)	96 (85.0)	111 (91.0)
Drug-related	15 (13.0)	9 (8.0)	13 (10.7)
Serious	13 (11.3)	13 (11.5)	15 (12.3)
Serious drug-related	0	0	1 (0.8)
No. (%) of women withdrawn from therapy due to AE	5 (4.3)	1 (0.9)	3 (2.5)
Drug-related	3 (2.6)	0	1 (0.8)
Serious	2 (1.7)	0	0

[a] Previously treated with 20 mg alendronate for 2 yr and 5 mg alendronate for 3 yr.

TABLE 3. Gastrointestinal (GI) adverse experiences (AE) by treatment group during yr 6–7

AE	Placebo (n = 115)[a]	5 mg alendronate (n = 113)	10 mg alendronate (n = 122)
No. (%) of women with UGI AE (≥1)	21 (18.3)	18 (15.9)	21 (17.2)
Drug-related	11 (9.6)	5 (4.4)	9 (7.4)
Withdrew due to AE	2 (1.7)	0	1 (0.8)
Withdrew due to drug-related AE	2 (1.7)	0	1 (0.8)

[a] Previously treated with 20 mg alendronate for 2 yr and 5 mg alendronate for 3 yr.

The study was not designed to compare fracture incidence between groups. Comparisons are complicated by the fact that all three groups were receiving alendronate or had received alendronate in the past. The incidence of vertebral and nonvertebral fractures (reported as adverse events) did not appear to increase within 2 yr after discontinuing alendronate, and the incidence of both types of fractures was similar in all three groups. During this 2-yr extension study, nine (7.8%), eight (7.1%), and eight (6.6%) patients had a nonvertebral fracture in the 20/5/PBO, 5 mg, and 10 mg groups, respectively. Eight (7.0%), seven (6.2%), and eight (6.6%) patients had a vertebral fracture adverse experience in the 20/5/PBO, 5 mg, and 10 mg groups, respectively. Moreover, there were no significant differences for changes in stature among the three groups during yr 6 and 7. The mean rate of decrease in stature was 1.2 mm/yr. During the first 3 yr of the study, the mean decrease in all patients treated with alendronate was 1.0 mm/yr, significantly lower ($P = 0.005$) than the 1.5 mm/yr decrease in the placebo group (9).

Discussion

Long-term treatment with antiresorptive therapy is probably needed by many patients, as current drugs for treatment of osteoporosis do not fully restore bone mass to healthy young adult levels. Therefore, the results of our study have important implications for treating osteoporotic patients with alendronate. Bone density continued to increase over time at the spine throughout the entire 7-yr study, suggesting that there may be a sustained effect on remodeling balance, and spine BMD might continue to increase with ongoing therapy. Increases in femoral neck and trochanter BMD were maintained over the 2-yr extension. Increasing BMD is especially important when treating older women; at any given BMD level, older women have higher fracture risk than younger women, and fracture risk is lower among women with higher BMD. There is also evidence that greater increases in BMD during antiresorptive treatment are associated with reduced fracture risk (17, 18). Our results indicate that long-term alendronate treatment provides relatively large and progressive increases in spinal BMD, stable increases in BMD at other sites, and stable reductions in biochemical markers. Thus, long-term alendronate treatment provides better skeletal benefits than shorter periods of treatment. These benefits were above and beyond any effect of calcium, as both the placebo and alendronate groups received calcium supplements.

Once incorporated into mineralized bone, alendronate has a long residence with a half-life measured in years, similar to calcium and other bone minerals. Osteoclasts may resorb less bone when they encounter alendronate in mineralized tissue. Alendronate released during bone resorption may also enter the circulation, where it would be available to inhibit bone resorption at other remodeling sites. Thus, it is possible that the alendronate present in bone from the previous 5 yr of treatment in the 20/5/PBO group may have slowed the rate of BMD declines in yr 6–7 (after discontinuation). Although the current study suggests that discontinuation of alendronate may result in some reversal of skeletal benefits, the effect is much less than that observed after estrogen withdrawal (19, 20).

BMD remained relatively stable over 2 yr after stopping alendronate in this study, although there was a small rise in bone turnover, as measured by NTX and BSAP. Similar findings have been reported in two other studies of alendronate discontinuation over 1 yr (20, 21). In contrast, estrogen discontinuation results in a rapid decline in BMD and increase in bone turnover (20, 22, 23). A substantial increase in bone turnover may have a deleterious effect on fracture risk, as the additional resorption pits may create local areas of weakness in trabeculae or perforate trabecular struts with irreparable damage (17). This may explain why the antifracture efficacy of estrogen diminishes markedly or disappears within several years after discontinuing estrogen treatment (24, 25).

Interpreting the incidence of new fractures and stature loss in the current study is complicated by the lack of a continuous placebo group. However, there is no evidence of an increase in fractures or height loss upon discontinuing alendronate compared to those in subjects continuing alendronate. There is some concern that excessive inhibition of bone

turnover might impair bone strength and increase fracture risk. For example, a recent study of dogs found that microcracks accumulated in the ribs of dogs treated with 5 times the usual human dose of risedronate and alendronate (26). Cortical remodeling was suppressed up to 68% compared to that in untreated dogs. However, the relevance to humans is unknown, because this study did not use a high turnover osteoporosis model and unusually high doses were used. In an ovariectomized baboon model of high turnover, alendronate reduced turnover to control (nonovariectomized) levels or lower, and increased BMD, resulting in an increase in bone strength (27). Among human patients treated with alendronate, bone turnover markers return to within the premenopausal range and are not excessively suppressed. Thus, continued monitoring of long-term safety is prudent, but existing evidence indicates that there is a considerably wide safety margin of decreased bone turnover, and that alendronate treatment reduces the risk of osteoporotic fractures (28).

The average increase in BMD compared to placebo during the initial 2 yr of this trial was nearly 7% during treatment with 10 mg alendronate daily and about 5% with 5 mg daily. These findings are very consistent with those reported previously for these doses (9–12). During 7 yr of treatment with 10 mg alendronate daily, spine BMD increased from baseline (month 0) by an average of 11%. Although there was no continuous placebo group for comparison during the final 2 yr, a progressive decline in BMD of 0.5–1%/yr would be expected for such a group from previous experience in clinical trials and epidemiological studies (1–4, 9). Although increases in soft tissue calcification with age may sometimes cause spine BMD to be overestimated, the original placebo group in this study lost approximately 1–2% at all measured sites during the first 3 yr, and there was no evidence of an increase in BMD during yr 6–7 in the 20/5/PBO group (9). As a result, the expected difference for 10 mg alendronate relative to placebo would be greater than 11% after 7 yr.

The mechanism by which inhibition of resorption by alendronate increases BMD rather than simply prevents further declines is not completely understood. The current theory is that the amount of bone resorbed is less than the amount subsequently formed, leading to continued positive bone balance and increases in BMD beyond the 1–2 yr needed to refill existing resorption sites in some studies (29–32). The current study indicates that increases in spine BMD may continue for at least 7 yr. Inhibiting excessive resorption may also allow compromised bone to respond to mechanical demands, preferentially thickening critical trabeculae, and helping to compensate for reduced connectivity (29, 33). Furthermore, reducing the rate of bone turnover allows more complete mineralization of bone tissue (34, 35). Each of these three mechanisms would increase BMD and might also improve bone strength and reduce fracture risk (17).

Two recent independent meta-analyses of all long-term, placebo-controlled clinical trials of antiresorptive drugs concluded that larger increases in BMD during antiresorptive therapy are associated with greater reductions in vertebral fracture risk (17, 36). Based on the relationship observed, a BMD increase of 12–14% (*vs.* placebo, as predicted after 7 yr of alendronate treatment) would correspond to as much as a 64% reduction in fracture risk.

Limited data are available regarding the long-term efficacy of other antiresorptive agents in randomized trials. Up to 7 yr of follow-up have been reported for a smaller study of cyclical etidronate therapy, with 3 yr of blinded treatment followed by 2 yr of open label treatment and 2 additional yr of blinded treatment (31). Women who received cyclical etidronate continuously for the full 7 yr (n = 51) had final BMD values approximately 7.5% above baseline. Bone density appeared to remain stable at the spine and hip for up to 2 yr after discontinuation of 5 yr of etidronate treatment (n = 46).

Most long-term clinical trials of estrogen have involved early postmenopausal women, and therefore may not be comparable to our findings. One open label (double blind for the first 2 yr) study of women less than 2 yr postmenopause reported the effect of 2 mg estradiol (plus progestin) daily for 10 yr on BMD of the spine and distal forearm (37). However, a large proportion (50–61%) of women dropped out, and the analysis was not by intention to treat. Among those who remained on treatment or placebo for 10 yr (n = 64), spine BMD increased 13.1% compared to a −4.7% loss in the untreated group, and forearm BMD remained stable at −0.7% compared to a 17.6% loss. A second study (n = 129 completed) reported the effect of high dose (2.5 mg conjugated estrogen, 2–4 times the currently recommended dose) estrogen treatment for 10 yr on bone mass at the metacarpal among women without osteoporosis (38). Women less than 3 yr postmenopause had increases of 8.7% at the metacarpal, but women more than 3 yr postmenopause had no increase relative to baseline; women taking placebo had BMD declines of approximately 10% (38). A study of mestranol treatment of ovariectomized women (n = 58) reported slight decreases in metacarpal (−1.9%) and radius (−2.2%) bone mass after an average of 9 yr of follow-up; bone mass changes in the placebo group (n = 42) were −9.5% at the radius and −13.9 at the metacarpal (39). As with the other estrogen studies, intention to treat analysis was not performed. A 5-yr open label study of women 2 yr or less postmenopause reported an 0.8% increase in spine BMD and a 1.4% decrease at the hip among 232 women receiving estrogen, compared to decreases of 4.3–4.5% in the placebo group (n = 116) (40).

Thus, our findings suggest that of the agents with long-term data (alendronate, etidronate, estrogen), alendronate yields the best demonstrated large increases in BMD among women with osteoporosis. These increases with alendronate are consistent across trials and progressive at the spine through 7 yr. Increases in BMD at the hip, total body, and forearm during the first few years are maintained in later years, even with discontinuation of therapy. Changes in biochemical markers were not available in other studies for comparison.

It is important to increase or preserve BMD for the purpose of reducing fracture risk among women with osteoporosis or osteopenia (17, 18). Estrogen may increase BMD initially, but there is evidence that long-term estrogen use may only slow bone loss (19, 38, 40). Epidemiological studies suggest that at least 6 yr of estrogen treatment may be required to achieve a significant reduction in fracture risk (24, 25, 42). This may partly explain why some women taking estrogen were found to have low BMD and experience fractures (43, 44). As a result, the National Osteoporosis Foundation recommends that BMD be measured in women who have been using

estrogen for long periods (3). Recent studies also show that addition of alendronate can augment BMD increases among estrogen-treated women whose BMD values remain in the osteoporotic range (45, 46).

We conclude that spinal BMD continues to increase throughout 7 yr of alendronate treatment, and BMD remains stable at other sites after rising during the first few years. Biochemical markers of bone turnover remained stable during the sixth and seventh years of treatment with alendronate, well below baseline. Bone density remained stable for 2 yr after discontinuing alendronate. Although there was a small increase in biochemical markers of bone turnover when treatment was discontinued, turnover remained well below baseline levels. The safety and tolerability of alendronate in yr 6 and 7 were similar to those of placebo. These findings should reassure clinicians that long-term alendronate treatment is very effective and generally well tolerated through at least 7 yr. The results indicate that discontinuation does not lead to accelerated bone loss as seen with estrogen, so accrued BMD gains will continue to play a role, as will the lower levels of bone turnover.

References

1. **Kanis JA, Delmas P, Burckhardt P, Cooper C, Torgerson D.** 1997 Guidelines for diagnosis and management of osteoporosis. Osteop Int. 7:390–406.
2. **Meunier P, Delmas P, Eastell R, et al.** 1999 Diagnosis and management of osteoporosis in postmenopausal women: guidelines for clinicians. Clin Ther. 21:1025–1044.
3. **National Osteoporosis Foundation.** 1998 Physician's guide to prevention and treatment of osteoporosis. Belle Mead: Excerpta Medica.
4. **Ross PD.** 1996 Osteoporosis: frequency, consequences, and risk factors. Arch Intern Med. 156:1399–1411.
5. **Doube A.** 1999 Managing osteoporosis in older people with fractures. Needs to be taken as seriously as coronary artery disease. Br Med J. 318:477–478.
6. **Johnell O.** 1997 The socioeconomic burden of fractures: today and in the 21st century. Am J Med. 103:20S–26S.
7. **Garnero P, Sornay-Rendu E, Chapuy M-C, et al.** 1996 Increased bone turnover in late postmenopausal women is a major determinant of osteoporosis. J Bone Miner Res. 11:337–349.
8. **Hochberg MC.** Preventing fractures in postmenopausal women with osteoporosis: a review of recent controlled trials of antiresorptive agents. Drugs Aging. In press.
9. **Liberman UA, Weiss SR, Broll J, et al.** 1995 Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. N Engl J Med. 333:1437–1443.
10. **Pols HAP, Felsenberg D, Hanley DA, et al.** 1999 Multinational, placebo-controlled, randomized trial of the effects of alendronate on bone density and fracture risk in postmenopausal women with low bone mass: results of the FOSIT study. Osteop Int. 9:461–468.
11. **Black DM, Cummings SR, Karpf DB, et al.** 1996 Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Lancet. 348:1535–1541.
12. **Cummings SR, Black DM, Thompson DE, et al.** 1998 Effect of alendronate on risk of fracture in women with low bone density but without vertebral fractures: results from the Fracture Intervention Trial. J Am Med Assoc. 280:2077–2082.
13. **Meunier PJ.** 1999 Evidence-based medicine and osteoporosis: A comparison of fracture risk reduction data from osteoporosis randomised clinical trials. Int J Clin Pract. 53:122–129.
14. **Black DM, Thompson DE, Bauer D, et al.** 2000 The early antifracture efficacy of alendronate in women with osteoporosis: results from Fracture Intervention Trial [Abstract]. Bone. 26(Suppl 3):B24.
15. **Levis S, Thompson D, Schneider DL, et al.** 1999 Alendronate reduces the risk of multiple clinical fractures: results from FIT [Abstract]. J Bone Miner Res. 14(Suppl 1):S527.
16. **Favus M, Emkey R, Leite M, et al.** 1997 Five-year treatment of osteoporosis in postmenopausal women with oral alendronate: effects on bone mass and turnover and safety [Abstract]. J Bone Miner Res. 12(Suppl 1):S150.
17. **Wasnich RD, Miller PD.** 2000 Antifracture efficacy of antiresorptive treatments are related to changes in bone density. J Clin Endocrinol Metab. 85:231–236.
18. **Hochberg M, Ross PD, Black D, et al.** 1999 Larger increases in bone mineral density during alendronate therapy are associated with a lower risk of new vertebral fractures in women with postmenopausal osteoporosis. Arthritis Rheum. 42:1246–1254.
19. **Davis JW, Ross PD, Johnson NE, Wasnich RD.** 1995 Estrogen and calcium supplement use among Japanese-American women: effects upon bone loss when used singly and in combination. Bone. 17:369–373.
20. **Greenspan SL, Bell N, Bone H, et al.** 1999 Differential effects of alendronate and estrogen on the rate of bone loss after discontinuation of treatment [Abstract]. J Bone Miner Res. 14(Suppl 1):S158.
21. **Stock JL, Bell NH, Chesnut III CH, et al.** 1997 Increments in bone mineral density of the lumbar spine and hip and suppression of bone turnover are maintained after discontinuation of alendronate in postmenopausal women. Am J Med. 103:291–297.
22. **Lindsay R, Hart DM, MacLean A, et al.** 1978 Bone response to termination of oestrogen treatment. Lancet. 1:1325–1327.
23. **Guanabens N, Spain B, Stuckey B, et al.** 1999 Alendronate (ALN) reverses bone loss associated with discontinuation of hormone replacement therapy. Calcif Tissue Int. 64(Suppl 1):S77.
24. **Schneider DL, Barrett-Connor EL, Morton DJ.** 1997 Timing of postmenopausal estrogen for optimal bone mineral density: the Rancho Bernardo study. J Am Med Assoc. 277:543–547.
25. **Michaelsson K, Baron JA, Farahmand BY, et al.** 1998 Hormone replacement therapy and risk of hip fracture: population based case-control study. Br Med J. 316:1858–1863.
26. **Mashiba T, Hirano T, Turner CH, Forwood MR, Johnston Jr CC, Burr DB.** 2000 Suppressed bone turnover by bisphosphonates increases microdamage accumulation and reduces some biomechanical properties in dog rib. J Bone Miner Res. 15:613–620.
27. **Balena R, Toolan BC, Shea M, et al.** 1993 The effects of 2-year treatment with the aminobisphosphonate alendronate on bone metabolism, bone histomorphometry, and bone strength in ovariectomized nonhuman primates. J Clin Invest. 92:2577–2586.
28. **Weinstein RS.** 2000 True strength. J Bone Miner Res. 15:621–625.
29. **Rodan G.** 1997 Bone mass homeostasis and bisphosphonate action. Bone. 20:1–4.
30. **Heaney RP, Yates AJ, Santora AC.** 1997 Bisphosphonate effects and the bone remodeling transient. J Bone Miner Res. 12:1143–1151.
31. **Miller PD, Watts NB, Licata AA, et al.** 1997 Cyclical etidronate in the treatment of postmenopausal osteoporosis: efficacy and safety after seven years of treatment. Am J Med. 103:468–476.
32. **Lane NE, Haupt D, Kimmel DB, Modin G, Kinney JH.** 1999 Early estrogen replacement therapy reverses the rapid loss of trabecular bone volume and prevents further deterioration of connectivity in the rat. J Bone Miner Res. 14:206–214.
33. **Kinney JH, Hyttinen PJ, Ladd AJC, Ryaby JT, Lane NE.** 1998 Trabecular thickening may compensate for reduced connectivity in human trabecular bone [Abstract]. Bone. 23(Suppl 5):S635.
34. **Parfitt AM.** 1993 Bone age, mineral density, and fatigue damage. Calcif Tissue Int. 53(Suppl 1):S82–S86.
35. **Meunier PJ, Boivin G.** 1997 Bone mineral density reflects bone mass but also the degree of mineralization of bone: therapeutic implications. Bone. 21:373–377.
36. **Black DM, Pearson J, Harris F, et al.** 1999 Predicting the effect of antiresorptive treatments on risk of vertebral fractures: a meta-analysis [Abstract]. J Bone Miner Res. 14(Suppl 1):S137.
37. **Eiken P, Kolthoff N, Pors Nielsen S.** 1996 Effect of 10 years' hormone replacement therapy on bone mineral content in postmenopausal women. Bone. 19(Suppl 5):191S–193S.
38. **Nachtigall LE, Nachtigall RH, Nachtigall RD, et al.** 1979 Estrogen replacement therapy. I. Ten year prospective study in the relationship to osteoporosis. Obstet Gynecol. 53:277–281.
39. **Lindsay R, Hart DM, Forrest C, Baird C.** 1980 Prevention of spinal osteoporosis in oophorectomised women. Lancet. 2:1151–1154.
40. **Komulainen MH, Kroger H, Tuppurainen MT, et al.** 1998 HRT and Vit D in prevention of non-vertebral fractures in postmenopausal women; a 5 year randomized trial. Maturitas. 31:45–54.
41. **Deleted in proof.**
42. **Colson F, Conrozier T, Tebib JG, et al.** 1998 Hormonal replacement therapy (HRT): Which duration is effective to reduce the incidence of fracture in postmenopausal women [Abstract]? Bone. 23(Suppl 5):S496.
43. **Nelson H, Harris E, Cauley J, et al.** 1998 Osteoporosis and fractures are common in older postmenopausal women taking estrogen [Abstract]. Bone. 23(Suppl 5):S152.
44. **Barrett-Connor E, Miller P, Faulkner K, et al.** 1998 The long term effects of estrogen therapy on bone mineral density: evidence from the National Osteoporosis Risk Assessment (NORA) Program [Abstract]. Bone. 23(Suppl 5):S390.
45. **Greenspan S, Bankhurst A, Bell N, et al.** 1999 Effects of alendronate and estrogen, alone or in combination, on bone mass and turnover in postmenopausal osteoporosis [Abstract]. Calcif Tissue Int. 64(Suppl 1):S79.
46. **Lindsay R, Cosman F, Lobo RA, et al.** 1999 Addition of alendronate to ongoing hormone replacement therapy in the treatment of osteoporosis: a randomized, controlled clinical trial. J Clin Enocrinol Metab. 84:3076–3081.