

## ALENDRONATE FOR THE PREVENTION AND TREATMENT OF GLUCOCORTICOID-INDUCED OSTEOPOROSIS

KENNETH G. SAAG, M.D., RONALD EMKEY, M.D., THOMAS J. SCHNITZER, M.D., PH.D., JACQUES P. BROWN, M.D., FEDERICO HAWKINS, M.D., STEFAN GOEMAERE, M.D., GORM THAMSBORG, M.D., URI A. LIBERMAN, M.D., PH.D., PIERRE D. DELMAS, M.D., PH.D., MARIE-PIERRE MALICE, PH.D., MICHELLE CZACHUR, M.P.H., AND ANASTASIA G. DAIFOTIS, M.D., FOR THE GLUCOCORTICOID-INDUCED OSTEOPOROSIS INTERVENTION STUDY GROUP\*

### ABSTRACT

**Background** Osteoporosis is a common complication of long-term glucocorticoid therapy for which there is no well-proved preventive or restorative treatment.

**Methods** We carried out two 48-week, randomized, placebo-controlled studies of two doses of alendronate in 477 men and women, 17 to 83 years of age, who were receiving glucocorticoid therapy. The primary end point was the difference in the mean percent change in lumbar-spine bone density from base line to week 48 between the groups. Secondary outcomes included changes in bone density of the hip, biochemical markers of bone turnover, and the incidence of new vertebral fractures.

**Results** The mean ( $\pm$ SE) bone density of the lumbar spine increased by  $2.1\pm 0.3$  percent and  $2.9\pm 0.3$  percent, respectively, in the groups that received 5 and 10 mg of alendronate per day ( $P<0.001$ ) and decreased by  $0.4\pm 0.3$  percent in the placebo group. The femoral-neck bone density increased by  $1.2\pm 0.4$  percent and  $1.0\pm 0.4$  percent in the respective alendronate groups ( $P<0.01$ ) and decreased by  $1.2\pm 0.4$  percent in the placebo group ( $P<0.01$ ). The bone density of the trochanter and total body also increased significantly in the patients treated with alendronate. There were proportionally fewer new vertebral fractures in the alendronate groups (overall incidence, 2.3 percent) than in the placebo group (3.7 percent) (relative risk, 0.6; 95 percent confidence interval, 0.1 to 4.4). Markers of bone turnover decreased significantly in the alendronate groups ( $P<0.001$ ). There were no differences in serious adverse effects among the three groups, but there was a small increase in nonserious upper gastrointestinal effects in the group receiving 10 mg of alendronate.

**Conclusions** Alendronate increases bone density in patients receiving glucocorticoid therapy. (N Engl J Med 1998;339:292-9.)

©1998, Massachusetts Medical Society.

**O**STEOPOROSIS is perhaps the most predictable and debilitating complication of long-term glucocorticoid therapy,<sup>1,2</sup> with bone loss that ultimately leads to fractures in up to 50 percent of patients.<sup>3-5</sup> Estrogen, vitamin D and its analogues, and calcitonin prevented bone loss in patients treated with glucocorticoids in some<sup>6-10</sup> but not all<sup>11-13</sup> studies. Recently, bisphosphonates have generated interest as a potential therapy

for glucocorticoid-induced osteoporosis because of their ability to inhibit bone resorption and their relatively few side effects.<sup>14</sup> In several studies of glucocorticoid-induced osteoporosis, pamidronate and etidronate increased spinal<sup>15-20</sup> and, to a lesser extent, hip<sup>17,18</sup> bone mineral density.

Alendronate is a potent bisphosphonate that increases the bone mineral density of the hip, spine, and total body<sup>21,22</sup> and lowers the incidence of vertebral, hip, and forearm fractures by approximately 50 percent in postmenopausal women with osteoporosis.<sup>21,23</sup> We report here the combined results of two double-blind, placebo-controlled, multicenter studies of the prevention and treatment of glucocorticoid-induced osteoporosis (one study in the United States and one in several other countries) that were nearly identical in design.

### METHODS

#### Patients

Men and women, 17 to 83 years of age, with underlying rheumatologic, pulmonary, dermatologic, gastrointestinal, or other diseases requiring long-term (at least one year) oral glucocorticoid therapy at a daily dose of at least 7.5 mg of prednisone or its equivalent were enrolled, irrespective of their base-line bone mineral density, in one of two parallel studies. One study involved 232 patients at 15 centers in the United States, and the other involved 328 patients at 22 centers in 15 other countries. The patients were stratified according to the duration of previous glucocorti-

From the Division of Rheumatology, Department of Internal Medicine, and the Department of Preventive Medicine and Environmental Health, University of Iowa College of Medicine, Iowa City (K.G.S.); the Bone Research Center, West Reading, Pa. (R.E.); Northwestern University, Chicago (T.J.S.); the Centre Hospitalier Universitaire de Quebec, Sainte-Foy, Que., Canada (J.P.B.); Servicio de Endocrinología, Hospital 12 de Octubre, Madrid (F.H.); University Hospital, Ghent, Belgium (S.G.); Osteoporosecentret Kommunehospitalet, Copenhagen, Denmark (G.T.); Beilison Medical Center, Petach-Tikva, Israel (U.A.L.); Hôpital Edouard Herriot, Lyons, France (P.D.D.); and Merck Research Laboratories, Rahway, N.J. (M.-P.M., M.C., A.G.D.). Address reprint requests to Dr. Saag at the Division of Rheumatology, Department of Internal Medicine, University of Iowa Hospitals and Clinics, 200 Hawkins Dr., Iowa City, IA 52242-1081.

Other authors were Nancy Lane, M.D. (University of California at San Francisco, San Francisco); Ricardo Correa-Rotter, M.D. (Instituto Nacional de la Nutrición, Salvador Zubiran, Mexico); Melissa Yanover, M.D. (Western Nephrology and Metabolic Bone Disease, Lakewood, Colo.); Rene Westhovens, M.D. (Universitair Ziekenhuis Leuven, Pellenberg, Belgium); Sol Epstein, M.D. (Albert Einstein Medical Center, Philadelphia); Jonathan D. Adachi, M.D. (St. Joseph's Hospital, McMaster University, Hamilton, Ont., Canada); Patrice Poubelle, M.D., D.Sc. (Centre Hospitalier Universitaire de Quebec, Sainte-Foy, Que., Canada); Jose Melo-Gomes, M.D. (Hospital Militar Principal, Unidade de Reumatologia, Lisbon, Portugal); and Jose A. Rodriguez-Portales, M.D. (Universidad Católica de Chile, Santiago, Chile).

\*Other members of the study group are listed in the Appendix.

coid therapy (less than 4 months, 4 to 12 months, or more than 12 months).

The exclusion criteria included evidence of metabolic bone disease (other than glucocorticoid-induced or postmenopausal osteoporosis), a low serum 25-hydroxyvitamin D concentration (<10 ng [25 nmol] per liter), concomitant therapy with drugs that affect bone turnover (e.g., a bisphosphonate, calcitonin, or fluoride), pregnancy or lactation, renal insufficiency (creatinine clearance rate, <35 ml per minute), severe cardiac disease, and a history of recent (within one year) major upper gastrointestinal disease. Patients with a history of gastrointestinal side effects from nonsteroidal antiinflammatory drugs agreed not to take such drugs during the study; otherwise their use was not restricted. Women receiving estrogen-replacement therapy continued taking the same dose throughout the study. The protocol was approved by the institutional review boards of the participating institutions, and all the patients provided informed consent.

### Treatment

Eighty-three patients from countries other than the United States were randomly assigned to receive 2.5 mg of oral alendronate daily, and 477 patients (from the United States and other countries) to receive 5 or 10 mg of oral alendronate or a matching placebo daily. All the patients were treated for 48 weeks. Each patient received 800 to 1000 mg of elemental calcium and 250 to 500 IU of vitamin D daily. The patients' primary physicians managed the glucocorticoid therapy during the study.

### Risk-Factor and Outcome Measurements

The patients were seen at base line and at 4, 12, 24, 36, and 48 weeks. They recorded their glucocorticoid dosage on diary cards, which were reviewed by the study staff at each visit. The self-reported base-line dietary calcium intake was estimated from a questionnaire that inquired about the consumption of various foods. The bone mineral density of the lumbar spine, hip, and total body was measured at base line and at 12, 24, 36, and 48 weeks by dual-energy x-ray absorptiometry with Hologic (Waltham, Mass.) or Lunar (Madison, Wis.) machines, and the results were analyzed by Medical Data Management (Waltham, Mass.). A standard phantom was used at all sites for cross-calibration. Serum and urine samples, obtained at base line and at 12, 24, 36, and 48 weeks for measurement of biochemical markers of bone turnover (serum bone-specific alkaline phosphatase concentrations and urinary excretion of cross-linked N-telopeptides of type I collagen corrected for the creatinine concentration), were analyzed at a central reference laboratory (Mayo Medical Laboratories, Rochester, Minn.).

Radiographs of the lateral lumbar and thoracic spine were taken at base line and at 48 weeks according to current guidelines<sup>24</sup> and were evaluated at a central facility (University of California, San Francisco). The measurement of changes in vertebral dimension by radiographic computerized digitization<sup>25</sup> was the primary method of assessing incident vertebral fractures, defined as decreases of  $\geq 20$  percent and  $\geq 4$  mm between base line and follow-up in anterior, middle, or posterior vertebral-body height (L1 to L5 and T4 to T12).<sup>23,25</sup>

A binary, semiquantitative visual assessment of the fractures was also performed.<sup>26</sup> The semiquantitative grading scale was as follows: grade 0, normal; grade 1, 20 to 25 percent reduction in height and 10 to 20 percent reduction in area; grade 2, 25 to 40 percent reduction in height and 20 to 40 percent reduction in area; and grade 3, 40 percent or greater reduction in height and area. In the binary assessment, vertebral fractures with grades of 2 or higher were defined as prevalent fractures, and fractures that increased in severity by at least one grade between base line and follow-up were defined as incident fractures.

The primary efficacy end point was the difference between groups in the percent change in lumbar-spine bone mineral density in the patients receiving  $\geq 7.5$  mg of prednisone (or its equivalent) daily at 48 weeks. Secondary efficacy end points were the percent

changes in hip and total-body bone mineral density, biochemical markers of bone turnover, and the incidence of fractures.

### Statistical Analysis

The combined results of the two studies were analyzed on an intention-to-treat basis. The main efficacy analysis was the percent change from base line to the last measurement of bone mineral density obtained while the patients were receiving at least 7.5 mg of prednisone (or its equivalent) per day. If no such measurement was available, the measurement of bone mineral density obtained at week 12 was used in the analysis. For analyses of biochemical markers we used the log-transformed fraction of the base-line value at week 48. The data from the patients who violated the protocol were excluded from these analyses.

Because the 2.5-mg dose of alendronate was used only in the multinational study, we discuss the results for this dose briefly in this report but analyze data only on the 477 patients assigned to 5 or 10 mg of alendronate or placebo. For the end points of clinical and biochemical efficacy, comparisons of placebo with the 5- and 10-mg doses of alendronate were made with the step-down Tukey trend test adjusted for multiplicity.<sup>27,28</sup> The analysis-of-variance model included as variables the treatment group, center, and stratum of previous glucocorticoid therapy. We assessed the possible differential treatment effects according to subgroups of interest (classified according to previous and current glucocorticoid therapy, underlying disease, age, sex, estrogen use, and base-line bone density) by testing the interactions between subgroup and treatment group in the analysis-of-variance model. All statistical tests were two-sided.

We tested for the presence of a treatment effect on the incidence of vertebral fractures using Fisher's exact test after combining the alendronate groups. The relative risk was calculated with a two-by-two contingency table.

We compared the percentages of patients having one or more adverse effects in the treatment groups by sequentially performing the Cochran-Armitage trend test with no adjustment for multiplicity.

## RESULTS

The characteristics of the 477 patients are shown in Table 1. Although the indications for and duration of glucocorticoid therapy varied, as did the patients' age, sex, and menopausal status, there were no significant differences in base-line characteristics among the treatment groups. Thirty-four percent of the postmenopausal women were taking estrogen-replacement therapy.

At base line, 34 percent of the patients had been treated with glucocorticoids for less than 4 months, 21 percent for 4 to 12 months, and the remaining 45 percent for more than 12 months. The median daily dose of glucocorticoid at base line was approximately 10 mg of prednisone (or its equivalent), and it did not differ significantly among the treatment groups. For the patients who remained in the study for 48 weeks (85 percent), the median daily glucocorticoid dose declined by week 48 to 9.0 mg of prednisone in the placebo group, 8.8 mg in the group receiving 5 mg of alendronate, and 8.7 mg in the group receiving 10 mg of alendronate; 67 percent of the patients were still receiving at least 7.5 mg of prednisone daily. During the study, the patients received a median cumulative dose of 3.3 g of prednisone (or its equivalent), a value that did not differ significantly among the treatment groups.

At base line, 43 percent of the patients had lum-

**TABLE 1. BASE-LINE CHARACTERISTICS OF THE STUDY PATIENTS.\***

CHARACTERISTIC	PLACEBO (N=159)	5 mg OF ALENDRONATE (N=161)	10 mg OF ALENDRONATE (N=157)
Age — yr	54±15	56±15	55±15
Estimated dietary calcium intake — mg/day	698±478	732±495	731±563†
Sex and menopausal status — no. (%)			
Men	52 (33)	45 (28)	44 (28)
Premenopausal women	40 (25)	34 (21)	30 (19)
Postmenopausal women	67 (42)	82 (51)	83 (53)
Race — no. (%)			
White	142 (89)	144 (89)	138 (88)
Other	17 (11)	17 (11)	19 (12)
Duration of prior glucocorticoid therapy — no. (%)			
<4 mo	52 (33)	54 (34)	54 (34)
4–12 mo	34 (21)	34 (21)	31 (20)
>12 mo	73 (46)	73 (45)	72 (46)
Underlying illness — no. (%)			
Rheumatoid arthritis	43 (27)	48 (30)	52 (33)
Polymyalgia rheumatica	24 (15)	37 (23)	30 (19)
Systemic lupus erythematosus	19 (12)	17 (11)	12 (8)
Pemphigus	12 (8)	15 (9)	10 (6)
Asthma	15 (9)	9 (6)	12 (8)
Inflammatory myopathy	10 (6)	8 (5)	7 (4)
Inflammatory bowel disease	8 (5)	6 (4)	10 (6)
Giant-cell arteritis	6 (4)	6 (4)	5 (3)
Sarcoidosis	5 (3)	3 (2)	7 (4)
Myasthenia gravis	12 (8)	2 (1)	1 (1)
Chronic obstructive pulmonary disease	3 (2)	6 (4)	4 (3)
Nephrotic syndrome	2 (1)	4 (2)	7 (4)
Daily glucocorticoid dose — mg of prednisone or equivalent			
Median	11‡	10	10‡
Range	5–120‡	8–135	7–95‡
Biochemical markers of bone turnover			
Mean urinary N-telopeptides of type I collagen — pmol of bone collagen equivalents/μmol of creatinine§	41±26¶	42±25	41±30‡
Serum bone-specific alkaline phosphatase — ng/ml**	10±5‡	10±5	10±4
Lumbar-spine bone mineral density — g/cm <sup>2</sup> ††			
Hologic system	0.95±0.16	0.92±0.17	0.93±0.16
Lunar system	1.03±0.21	1.02±0.15	1.06±0.20

\*Plus-minus values are means ±SD. There were no significant differences between treatment groups. Because of rounding, not all percentages total 100.

†Data for 156 of the 157 patients receiving 10 mg of alendronate were available for analysis.

‡Data for 158 of the 159 patients receiving placebo were available for analysis.

§The normal range is 0 to 131 pmol of bone collagen equivalents per micromole of creatinine.

¶Data for 155 of the 159 patients receiving placebo were available for analysis.

||Data for 160 of the 161 patients receiving 5 mg of alendronate were available for analysis.

\*\*The normal ranges are 4 to 17 ng per milliliter for men and 2 to 17 ng per milliliter for women.

††Data for 154 of the 159 patients receiving placebo, 154 of the 161 patients receiving 5 mg of alendronate, and 153 of the 157 patients receiving 10 mg of alendronate were available for analysis. According to the two systems used to measure lumbar-spine bone mineral density, 1 SD below the mean for young adults was as follows: for the Hologic system, 0.98 g per square centimeter for men and 0.94 g per square centimeter for women; for the Lunar system, 1.10 g per square centimeter for men and 1.06 g per square centimeter for women.

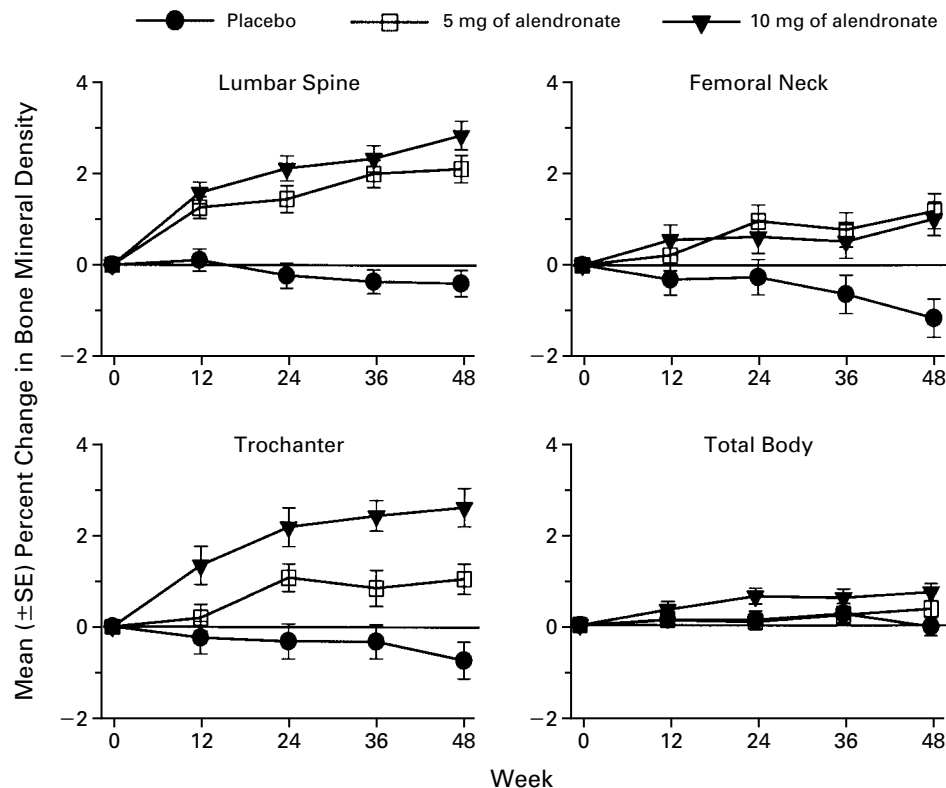
bar-spine bone mineral density within 1 SD of the peak value for sex-matched healthy young adults, and 32 percent had osteoporosis, as defined by a lumbar-spine bone mineral density more than 2 SD below the peak value for healthy young adults. The proportions did not differ significantly between the placebo and alendronate groups.

Overall, the base-line mean dietary calcium intake was 720 mg per day, and more than 96 percent of

the patients maintained a daily calcium intake (including supplements) of at least 1000 mg (median, 1584) during the study.

#### Bone Mineral Density

At 48 weeks, the mean (±SE) bone mineral density in the groups receiving 5 or 10 mg of alendronate was significantly increased at the lumbar spine, trochanter, and femoral neck, and total-body bone



**Figure 1.** Effects of Alendronate on Bone Mineral Density in All Patients Receiving an Average Daily Dose of at Least 7.5 mg of Prednisone (or Its Equivalent).

mineral density was significantly increased in the group receiving 10 mg (Fig. 1 and Table 2). The patients taking 2.5 mg of alendronate had a small, nonsignificant increase in lumbar-spine bone mineral density ( $0.7 \pm 0.4$  percent). The increases in bone mineral density did not differ according to the glucocorticoid dose or the lumbar-spine bone mineral density at base line. Approximately 80 percent of the patients in the alendronate groups had increases in lumbar-spine bone mineral density, as compared with 45 percent of those in the placebo group.

The increase in lumbar-spine bone mineral density was higher in the postmenopausal women not taking estrogen who received 10 mg of alendronate than in the other subgroups (Table 2). However, the duration of previous glucocorticoid therapy did not affect the response to alendronate (Table 2), nor did the underlying disease (data not shown). The lumbar-spine bone mineral density in the patients treated with either 5 or 10 mg of alendronate who were receiving high daily doses of glucocorticoids (mean, 23.5 mg of prednisone or its equivalent) for bullous skin diseases increased by 2 percent from base line, as compared with a decrease of 3 percent in the patients receiving placebo, for a total difference of 5 percent (data not shown).

#### Biochemical Markers of Bone Turnover

Urinary excretion of N-telopeptides of type I collagen decreased by 60 percent and serum bone-specific alkaline phosphatase concentrations decreased by 27 percent in the alendronate groups (Fig. 2). Among the patients in the alendronate groups there were no significant differences in these changes in biochemical markers of bone turnover according to sex, menopausal status, or estrogen therapy.

#### Fractures

Seventeen percent of the patients in the placebo group and 15 percent of those in the alendronate groups had vertebral fractures at base line. New fractures during the study were uncommon (Table 3), and the incidence of morphometrically defined vertebral fractures in the alendronate groups (5 and 10 mg combined) was not significantly lower than that in the placebo group (relative risk, 0.6; 95 percent confidence interval, 0.1 to 4.4). A post hoc analysis of semiquantitatively determined incident vertebral fractures revealed no significant difference in overall incidence between the alendronate and placebo groups ( $P=0.18$ ). The majority of the vertebral fractures occurred in postmenopausal women, in whom there was a difference of borderline significance be-

**TABLE 2. PERCENT CHANGE IN BONE MINERAL DENSITY FROM BASE LINE TO WEEK 48 ACCORDING TO SITE, SEX, MENOPAUSAL STATUS, AND DURATION OF PREVIOUS GLUCOCORTICOID THERAPY.\***

SITE	PLACEBO		5 mg OF ALENDRONATE		10 mg OF ALENDRONATE	
	NO. OF PATIENTS	PERCENT CHANGE	NO. OF PATIENTS	PERCENT CHANGE	NO. OF PATIENTS	PERCENT CHANGE
Lumbar spine	142	-0.4±0.3	146	+2.1±0.3†‡	145	+2.9±0.3†‡
Sex and menopausal status§						
Men	49	-0.7±0.4	40	+3.4±0.6	41	+2.9±0.5
Premenopausal women	35	-0.3±0.7	30	+2.0±0.6	29	+2.0±0.6
Postmenopausal women receiving estrogen¶	18	-0.6±0.9	27	+1.6±0.7	25	+1.5±0.6
Postmenopausal women not receiving estrogen	40	-0.1±0.6	49	+1.5±0.5	50	+4.0±0.6
Duration of prior glucocorticoid therapy						
<4 mo	47	-1.0±0.6	51	+1.4±0.6	53	+3.0±0.6
4-12 mo	29	-0.6±0.6	30	+2.4±0.5	29	+2.8±0.6
>12 mo	66	+0.2±0.4	65	+2.5±0.4	63	+2.8±0.4
Femoral neck	142	-1.2±0.4**	146	+1.2±0.4†**	145	+1.0±0.4†**
Trochanter	142	-0.7±0.4	146	+1.1±0.3**††	145	+2.7±0.4†‡
Total body	109	-0.03±0.2	110	+0.4±0.2	113	+0.7±0.2†††

\*Plus-minus values are means ±SE.

†P≤0.001 for the comparison with the base-line values.

‡P≤0.001 for the comparison with placebo.

§P=0.02 for the interaction between treatment and subgroup.

¶Estrogen was taken orally or transdermally for at least 50 percent of the time the women were participating in the study.

||P>0.10 for the interaction between treatment and subgroup.

\*\*P≤0.01 for the comparison with the base-line values.

††P≤0.01 for the comparison with placebo.

tween those receiving alendronate and those receiving placebo (P=0.05).

The incidence of nonvertebral fractures was identical in the alendronate and placebo groups (4.4 percent); the most common sites were the ribs and forearm.

#### Adverse Effects

The incidence of adverse effects that were considered serious or that led to withdrawal from the study was similar in the alendronate and placebo groups (Table 4). The most common adverse effects were musculoskeletal pain (16 percent in the placebo group vs. 14 percent and 16 percent in the groups receiving 5 and 10 mg of alendronate, respectively), upper respiratory infection (9 percent vs. 12 and 13 percent), headache (6 percent vs. 8 and 8 percent), and urinary tract infection (8 percent vs. 10 and 6 percent). Upper gastrointestinal adverse effects (mainly abdominal pain) were more common in the patients who received 10 mg of alendronate than in the other two groups, but they rarely resulted in study discontinuation. Despite concurrent therapy with glucocorticoids, nonsteroidal antiinflammatory drugs, or aspirin (in 45 percent of all patients), there was no increase in esophageal adverse effects or peptic ulcers in the alendronate groups.

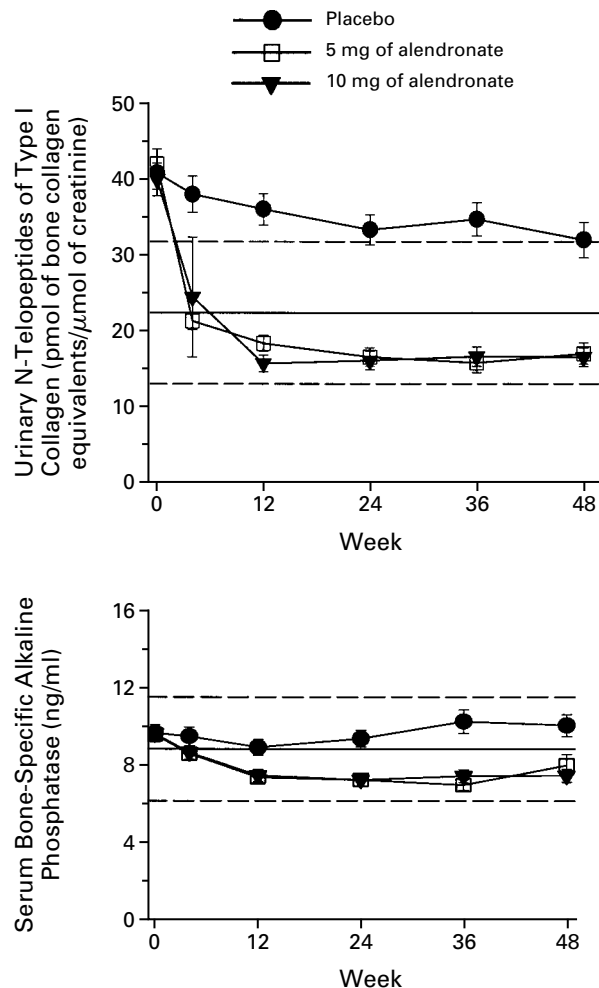
#### DISCUSSION

We found that alendronate significantly increased lumbar-spine, hip, and total-body bone mineral density in patients receiving glucocorticoid therapy. The efficacy of alendronate did not vary significantly according to the previous duration or current dose of glucocorticoid therapy, a finding that supports its use for both preventing and treating glucocorticoid-induced osteoporosis. We studied patients taking glucocorticoids for a variety of underlying disorders, a fact that suggests that our results can be generalized to the overall population of patients receiving long-term glucocorticoid therapy.<sup>31</sup>

An unexpected finding was the minimal loss of lumbar-spine bone mass among the patients in the placebo group. However, these patients received ample calcium and vitamin D supplementation and had a relatively high base-line dietary calcium intake. The small loss in bone mineral density in this group may be indicative of the potential beneficial effects of calcium and vitamin D in patients with glucocorticoid-induced osteoporosis.<sup>10</sup>

The reduction in bone turnover in our studies is consistent with the findings of other alendronate trials<sup>21,22</sup> and provides further evidence that alendronate slows osteoclastic bone resorption.

We studied too few patients to detect effects on



**Figure 2.** Effects of Alendronate on Biochemical Markers of Bone Resorption in 259 Patients (Top Panel) and Bone Formation in 264 Patients (Bottom Panel) Receiving an Average Daily Dose of at Least 7.5 mg of Prednisone (or Its Equivalent). All values are means ( $\pm$ SE). The solid horizontal lines indicate the mean reference values for premenopausal women, and the dotted horizontal lines 1 SD above and below the mean.<sup>29,30</sup> The values were significantly decreased at 48 weeks in the patients receiving 5 mg of alendronate and those receiving 10 mg ( $P < 0.001$ ).

the incidence of fracture. Nonetheless, there was a slight reduction in radiographically proved vertebral fractures in the patients treated with alendronate. Although not significant, the relative risk of vertebral fracture in this 48-week study lies within the 95 percent confidence intervals for the relative risks after 3 years in the Phase III Osteoporosis Treatment Study<sup>21</sup> and the Fracture Intervention Trial.<sup>23</sup> The majority of vertebral fractures (82 percent) were in postmenopausal women.

In a double-blind, placebo-controlled, randomized, multicenter trial, intermittent etidronate therapy prevented bone loss in patients treated with glucocorti-

**TABLE 3.** INCIDENCE OF VERTEBRAL FRACTURES.

METHOD	PLACEBO (N=159)	5 OR 10 mg OF ALENDRONATE (N=318)	
		no. with fractures/ no. who could be evaluated (%)	
<b>Quantitative morphometry*</b>			
All patients	5/134 (3.7)	6/266 (2.3)	
Men	1/48 (2.1)	1/74 (1.4)	
Premenopausal women	0	0	
Postmenopausal women	4/53 (7.6)	5/134 (3.7)	
<b>Binary semiquantitative assessment†</b>			
All patients	8/135 (5.9)	8/268 (3.0)	
Men	1/48 (2.1)	2/75 (2.7)	
Premenopausal women	0	0	
Postmenopausal women	7/54 (13)	6/135 (4.4)‡	

\*An incident fracture was defined by a decrease of  $\geq 20$  percent and  $\geq 4$  mm in vertebral height by quantitative morphometry.

†An incident fracture was defined by a change in grade of  $\geq 1$  from base line to follow-up by binary semiquantitative assessment.

‡ $P=0.05$  for the comparison with placebo.

coids.<sup>19</sup> Although a direct comparison is not possible, the percent increase in lumbar-spine bone mineral density at 52 weeks in the patients receiving etidronate was 0.6 percent, which is less than the increases in the patients treated with alendronate in our 48-week study. However, the loss was greater in the placebo group in the etidronate study (3.2 percent) than in the placebo group in our study (0.4 percent), so the differences between study drug and placebo were similar in the two studies. Although alendronate increased femoral-neck and trochanter bone density, etidronate had a protective effect only at the trochanter (but did not increase bone mineral density).<sup>19</sup> It is worth noting that new fractures developed in 15 percent of the patients in the placebo group in the etidronate study, as compared with only 3.7 percent in our study. This finding is consistent with the fact that the prevalence of vertebral fractures at base line was three times as high in the etidronate study and may also reflect the effects of higher doses of calcium and vitamin D in our study (the patients in the etidronate study received only 500 mg of calcium per day and no vitamin D supplement). A second, similarly designed multicenter trial of etidronate for the prevention of glucocorticoid-induced osteoporosis recently showed a significant protective effect at the lumbar spine but not at the trochanter or femoral neck, and there was no significant protection against fracture.<sup>20</sup>

In our study, alendronate caused few adverse effects. Upper gastrointestinal symptoms (mainly abdominal pain) were more common in the patients receiving 10 mg of alendronate, and were slightly more common in the patients receiving 5 mg of

TABLE 4. CLINICAL ADVERSE EFFECTS.

ADVERSE EFFECT	PLACEBO (N=159)	5 mg OF	10 mg OF
		ALENDRONATE (N=161)	ALENDRONATE (N=157)
no. of patients (%)			
Any adverse effect	126 (79)	129 (80)	131 (83)
Any serious adverse effect*	34 (21)	25 (16)	30 (19)
Withdrawal due to an adverse effect	8 (5)	8 (5)	6 (4)
Any upper gastrointestinal adverse effect†	26 (16)	30 (19)	40 (25)
Abdominal pain	8 (5)	9 (6)	15 (10)
Peptic ulcer‡	2 (1)	1 (1)	2 (1)
Esophageal irritation§	4 (3)	5 (3)	3 (2)
Any serious upper gastrointestinal adverse effect*	2 (1)	0	2 (1)

\*This category includes adverse effects requiring hospitalization, and those that were life-threatening or fatal.

† $P < 0.05$  by test for trend.

‡This category includes gastric, peptic, and duodenal ulcers.

§This category includes dysphagia, esophagitis, reflux esophagitis, and esophageal ulcer.

alendronate, than in those receiving placebo. These results, like those of other alendronate trials,<sup>21,22</sup> suggest that the rare lower esophageal adverse effects noted in reports of post-marketing surveillance<sup>32</sup> can be minimized by correct alendronate dosing.

In conclusion, for patients with glucocorticoid-induced osteoporosis or for those at high risk for it, the daily administration of alendronate significantly increases bone mineral density, the most important predictor of the risk of fracture at several sites.<sup>33</sup> The benefit we observed was not related to the age or sex of the patients, the underlying disease, or the dose of glucocorticoid. The efficacy of 5 and 10 mg of alendronate was similar, except in postmenopausal women not receiving estrogen therapy, in whom the higher dose was more effective.

Supported by grants from Merck & Company and the General Clinical Research Centers Programs, National Center for Research Resources, National Institutes of Health (RR00059).

Presented in part at the National Scientific Meeting of the American College of Rheumatology, Washington, D.C., November 8–12, 1997.

Drs. Saag, Emkey, Schnitzer, Brown, and Delmas have served as consultants to Merck & Company, the manufacturers of alendronate.

*We are indebted to Michael Nevitt, Ph.D., Ria San Valentin, M.D., and the Prevention Sciences Group of the University of California at San Francisco for their technical expertise in analyzing the spine radiographs.*

## APPENDIX

Other members of the Glucocorticoid-Induced Osteoporosis Intervention Study Group are as follows: **U.S. Study:** Bone Research Center, West Reading, Pa. — P. Moyer, G. Nuss, and D. Rohrbach; Albert Einstein Medical Center, Philadelphia — A. Salzman, J. Zack, G. Leggett, and B. Winer; University Hospital Medical Center, Stony Brook, N.Y. — B. Gruber, L. Kaufman, L. Titus, and L. Rannazi; University of Pennsylvania, Philadelphia — J. Haddad, H. Bazaraa, L. Loh, A. Tate, and S. Troupe; Mayo

Clinic, Rochester, Minn. — S. Hodgson, S. Khosla, S. LeBlanc, and D. Enright; Kaiser Permanente Center for Health Research, Portland, Oreg. — A. Hurtado, T. Vogt, B. Gandara, K. Schlaudecker, C. Romero, and R. Garza; Rosalind Russell Arthritis Research Laboratories, San Francisco — P. Mroczkowski, C. Merrifield, and R. Montanti; University of Iowa College of Medicine, Iowa City — R. Koehnke, J. Torner, M. Tullis, and R. Wallace; Northwestern University, Chicago — R. Balias and D. Olejniczak; Arizona Rheumatology Center, Phoenix — J. Tesser, O. Gluck, and D. Gray; Western Nephrology and Metabolic Bone Disease, Lakewood, Colo. — P. Miller, H. Hainault, and J. Kennedy; University of Pittsburgh Medical Center, Pittsburgh — M. Roberts, M. Santis, and J. Zmuda; Tampa Medical Group, Tampa, Fla. — H. McIlwain, J. Silverfield, M. Burnette, B. Germain, R. Altomose, J. LaPorte, and P. Kaufman; Oregon Osteoporosis Center, Portland — M. McClung, K. Cooke, and H. Volk; and Research Institute of Dallas, Dallas — S. Feld, T. Cook, and E. Morgan. **Multinational Study:** Hospital das Clinicas, Faculdade de Medicina da Universidade de São Paulo, São Paulo, Brazil — M. Leite, A. Borelli, E. Arioli, P. Correa, and L. Galina; Hôpital Edouard Herriot, Lyons, France — E. Confavreux, C. Hardouin, and F. Dubocuf; University Hospital, Ghent, Belgium — J.-M. Kaufman, S. Toye, and M. DeSchepper; Johannesburg Hospital, Parktown, South Africa — J. Wing, F. Raal, C. Schnitzler, S. Goldburgh, L. Wane, and A. Grisillo; Instituto Nacional Nutrición Salvador Zubirán, Mexico City, Mexico — S. Jasqui and M. Cortés; Academic Hospital, Uppsala, Sweden — S. Ljunghall, E. Bornefalk, and A. Thulin; Department of Rheumatology, Universitair Ziekenhuis Leuven, Pellenberg, Belgium — J. Dequeker, J. Joly, and J. Nijs; Osteoporosecentret Kommunehospitalet, Copenhagen, Denmark — O. Sorensen and A. Gam; Immanuel Krankenhaus, Berlin, Germany — J. Semler and I. Herrnenaba; Centre Hospitalier Universitaire de Québec, Sainte-Foy, Que., Canada — E. Lejeune, N. Gagné, and L. Mailloux; Unidade de Reumatologia, Hospital Militar Principal, Lisbon, Portugal — R. André-Santos and P. Mateus; St. Joseph Hospital, Hamilton, Ont., Canada — A. Cividino, W. Bensen, M. Gordon, J. Zahavich, and L. McMahon; University of Alberta, Edmonton, Canada — K. Siminoski, L. Creasy, and N. Gann; Praxis, Wiesbaden, Germany — E. Keck, C. Goehre, and G. Werner-Hoefner; Medizinische Klinik und Poliklinik, Dusseldorf, Germany — A. Becker and I. Heimlich; Universidad Católica de Chile, Santiago, Chile — V. Cervilla and A. Rojas; Medizinische Klinik III, Mainz, Germany — J. Beyer, P. Kann, B. Piepkorn, B. Ptock, and M. Bantelmann; Hospital 12 de Octubre, Madrid — L. Morillas, J. Padrino, and D. Puente; Belison Medical Center, Tel Aviv University, Petach-Tikva, Israel — R. Aric, M. David, N. Katzenlesson, H. Trau, and Z. Libman; Academisch Ziekenhuis, Leiden, the Netherlands — S. Papapoulos, N. Hamdy, and B. Sinon; Hôpital Cochin, Paris — C.-J. Menkes, C. Cormier, and E. Gallimard; and Austin and Repatriation Medical Center, Heidelberg, Australia — E. Seeman and S. Matthews.

## REFERENCES

1. Saag KG. Low-dose corticosteroid therapy in rheumatoid arthritis: balancing the evidence. *Am J Med* 1997;103:Suppl 6A:31S-39S.
2. Dequeker J, Westhovens R. Low dose corticosteroid associated osteoporosis in rheumatoid arthritis and its prophylaxis and treatment: bones of contention. *J Rheumatol* 1995;22:1013-9.
3. Lukert BP, Raisz LG. Glucocorticoid-induced osteoporosis: pathogenesis and management. *Ann Intern Med* 1990;112:352-64.
4. Michel BA, Bloch DA, Fries JF. Predictors of fractures in early rheumatoid arthritis. *J Rheumatol* 1991;18:804-8.
5. Adinoff AD, Hollister JR. Steroid-induced fractures and bone loss in patients with asthma. *N Engl J Med* 1983;309:265-8.
6. Hall GM, Daniels M, Doyle DV, Spector TD. Effect of hormone replacement therapy on bone mass in rheumatoid arthritis patients treated with and without steroids. *Arthritis Rheum* 1994;37:1499-505.
7. Hahn TJ, Halstead LR, Teitelbaum SL, Hahn BH. Altered mineral metabolism in glucocorticoid-induced osteopenia: effect of 25-hydroxyvitamin D administration. *J Clin Invest* 1979;64:655-65.
8. Verstraeten A, Dequeker J, Nijs J, Geusens P. Prevention of postmenopausal bone loss in rheumatoid arthritis patients: a two-year prospective study. *Clin Exp Rheumatol* 1989;7:351-8.
9. Sambrook P, Birmingham J, Kelly P, et al. Prevention of corticosteroid osteoporosis: a comparison of calcium, calcitriol, and calcitonin. *N Engl J Med* 1993;328:1747-52.
10. Buckley LM, Leib ES, Cartularo KS, Vacek PM, Cooper SM. Calcium and vitamin D3 supplementation prevents bone loss in the spine secondary to low-dose corticosteroids in patients with rheumatoid arthritis: a randomized, double-blind, placebo-controlled trial. *Ann Intern Med* 1996;125:961-8.
11. Dykman TR, Haralson KM, Gluck OS, et al. Effect of oral 1,25-dihydroxyvitamin D and calcium on glucocorticoid-induced osteopenia in patients with rheumatic diseases. *Arthritis Rheum* 1984;27:1336-43.
12. Healey JH, Paget SA, Williams-Russo P, et al. A randomized controlled trial of salmon calcitonin to prevent bone loss in corticosteroid-

- treated temporal arteritis and polymyalgia rheumatica. *Calcif Tissue Int* 1996;58:73-80.
13. Adachi JD, Bensen WG, Bianchi F, et al. Vitamin D and calcium in the prevention of corticosteroid induced osteoporosis: a 3 year followup. *J Rheumatol* 1996;23:995-1000.
14. Fleisch H. New bisphosphonates in osteoporosis. *Osteoporos Int* 1993;3:Suppl 2:S15-S22.
15. Reid IR, King AR, Alexander CJ, Ibbertson HK. Prevention of steroid-induced osteoporosis with (3-amino-1-hydroxypropylidene)-1,1-bisphosphonate (APD). *Lancet* 1988;1:143-6.
16. Adachi JD, Cranney A, Goldsmith CH, et al. Intermittent cyclic therapy with etidronate in the prevention of corticosteroid induced bone loss. *J Rheumatol* 1994;21:1922-6.
17. Diamond T, McGuigan L, Barbagallo S, Bryant C. Cyclical etidronate plus ergocalciferol prevents glucocorticoid-induced bone loss in postmenopausal women. *Am J Med* 1995;98:459-63.
18. Struys A, Snelder AA, Mulder H. Cyclical etidronate reverses bone loss of the spine and proximal femur in patients with established corticosteroid-induced osteoporosis. *Am J Med* 1995;99:235-42.
19. Adachi JD, Bensen WG, Brown J, et al. Intermittent etidronate therapy to prevent corticosteroid-induced osteoporosis. *N Engl J Med* 1997;337:382-7.
20. Roux C, Oriente P, Laan R, et al. Randomized trial of effect of cyclical etidronate in the prevention of corticosteroid-induced bone loss. *J Clin Endocrinol Metab* 1998;83:1128-33.
21. Liberman UA, Weiss SR, Bröll J, et al. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. *N Engl J Med* 1995;333:1437-43.
22. Chesnut CH III, McClung MR, Ensrud KE, et al. Alendronate treatment of the postmenopausal osteoporotic woman: effect of multiple dosages on bone mass and bone remodeling. *Am J Med* 1995;99:144-52.
23. Black DM, Cummings SR, Karpf DB, et al. Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. *Lancet* 1996;348:1535-41.
24. Kiel D. Assessing vertebral fractures: National Osteoporosis Working Group on Vertebral Fractures. *J Bone Miner Res* 1995;10:518-23. [Erratum, *J Bone Miner Res* 1995;10:1605.]
25. Jergas M, San Valentin R. Techniques for the assessment of vertebral dimensions in quantitative morphometry. In: Genant HK, Jergas M, van Kuijk C, eds. *Vertebral fracture in osteoporosis*. San Francisco: Radiology Research and Education Foundation, 1995:163-88.
26. Genant HK, Jergas M, Palermo L, et al. Comparison of semiquantitative visual and quantitative morphometric assessment of prevalent and incident vertebral fractures in osteoporosis. *J Bone Miner Res* 1996;11:984-96.
27. Tukey JW, Ciminera JL, Heyse JF. Testing the statistical certainty of a response to increasing doses of a drug. *Biometrics* 1985;41:295-301.
28. Capizzi T, Survill TT, Heyse JF, Malani H. An empirical and simulated comparison of some tests for detecting progressiveness of response with increasing doses of a compound. *Biom J* 1992;34:275-89.
29. Garnero P, Delmas PD. Assessment of serum levels of bone alkaline phosphatase with a new immunoradiometric assay in patients with metabolic bone disease. *J Clin Endocrinol Metab* 1993;77:1046-53.
30. Garnero P, Sornay-Rendu E, Delmas PD. Decreased bone turnover in oral contraceptive users. *Bone* 1995;16:499-503.
31. Walsh LJ, Wong CA, Pringle M, Tattersfield AE. Use of oral corticosteroids in the community and the prevention of secondary osteoporosis: a cross sectional study. *BMJ* 1996;313:344-6.
32. de Groen PC, Lubbe DF, Hirsch LJ, et al. Esophagitis associated with the use of alendronate. *N Engl J Med* 1996;335:1016-21.
33. Cummings SR, Black DM, Nevitt MC, et al. Bone density at various sites for prediction of hip fractures. *Lancet* 1993;341:72-5.

---

**RECEIVE THE *JOURNAL'S* TABLE OF CONTENTS EACH WEEK BY E-MAIL**

To receive the table of contents of the *New England Journal of Medicine* by e-mail every Thursday morning, send an e-mail message to:

**listserv@massmed.org**

Leave the subject line blank, and type the following as the body of your message:

**subscribe TOC-L**

You can also sign up through our Web site at: <http://www.nejm.org>

---