

## INTERMITTENT ETIDRONATE THERAPY TO PREVENT CORTICOSTEROID-INDUCED OSTEOPOROSIS

JONATHAN D. ADACHI, M.D., WILLIAM G. BENSON, M.D., JACQUES BROWN, M.D., DAVID HANLEY, M.D., ANTHONY HODSMAN, M.D., ROBERT JOSSE, M.D., DAVID L. KENDLER, M.D., BRIAN LENTLE, M.D., WOJCIECH OLSZYNSKI, M.D., LOUIS-GEORGE STE.-MARIE, M.D., ALAN TENENHOUSE, M.D., AND ARKADI A. CHINES, M.D.

### ABSTRACT

**Background and Methods** Osteoporosis is a recognized complication of corticosteroid therapy. Whether it can be prevented is not known. We conducted a 12-month, randomized, placebo-controlled study of intermittent etidronate (400 mg per day for 14 days) followed by calcium (500 mg per day for 76 days), given for four cycles, in 141 men and women (age, 19 to 87 years) who had recently begun high-dose corticosteroid therapy. The primary outcome measure was the difference in the change in the bone density of the lumbar spine between the groups from base line to week 52. Secondary measures included changes in the bone density of the femoral neck, trochanter, and radius and the rate of new vertebral fractures.

**Results** The mean ( $\pm$ SE) bone density of the lumbar spine and trochanter in the etidronate group increased  $0.61\pm 0.54$  and  $1.46\pm 0.67$  percent, respectively, as compared with decreases of  $3.23\pm 0.60$  and  $2.74\pm 0.66$  percent, respectively, in the placebo group. The mean differences between the groups after one year were  $3.72\pm 0.88$  percentage points for the lumbar spine ( $P=0.02$ ) and  $4.14\pm 0.94$  percentage points for the trochanter ( $P=0.02$ ). The changes in the femoral neck and the radius were not significantly different between the groups. There was an 85 percent reduction in the proportion of postmenopausal women with new vertebral fractures in the etidronate group as compared with the placebo group (1 of 31 patients vs. 7 of 32 patients,  $P=0.05$ ), and the etidronate-treated postmenopausal women also had significantly fewer vertebral fractures per patient ( $P=0.04$ ).

**Conclusions** Intermittent etidronate therapy prevents the loss of vertebral and trochanteric bone in corticosteroid-treated patients. (N Engl J Med 1997; 337:382-7.)

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HIGH-DOSE oral corticosteroid therapy is given to patients with a variety of medical conditions. Although often effective, corticosteroids commonly cause osteoporosis.<sup>1-3</sup> The degree or extent of bone loss is most closely correlated with the cumulative corticosteroid dose,<sup>4</sup> but the rate of bone loss is highest in the first three to six months of therapy, after which it slows. Nevertheless, the rate remains increased for as long as high-dose corticosteroid therapy continues.<sup>4,5</sup> Given the frequency and magnitude of the

problem of corticosteroid-induced osteoporosis, preventive therapy should be considered for patients who are expected to receive corticosteroid therapy for more than a few weeks.

Previous small and open-label studies have suggested that intermittent cyclic therapy with etidronate may prevent corticosteroid-induced osteoporosis.<sup>6,7</sup> Therefore, we performed a 12-month randomized, double-blind, placebo-controlled, multicenter study to determine the ability of intermittent cyclic therapy with etidronate to prevent corticosteroid-induced osteoporosis.

### METHODS

#### Subjects

Ambulatory patients, 18 to 90 years of age, with a variety of diseases were eligible for the study if they had started high-dose therapy with prednisone or its equivalent within the previous 100 days and were expected to continue treatment for at least 1 year at a mean daily dose of 7.5 mg or greater for 90 days, with subsequent ongoing treatment at a mean daily dose of 2.5 mg or greater (Table 1). Patients were excluded if they had abnormalities on spinal radiographs that precluded accurate measurements of the lumbar spine with dual-energy x-ray absorptiometry, or if they had diseases or had taken medications known to affect bone metabolism within the preceding year. None of the patients had taken corticosteroids in the past. All patients provided written informed consent, and the study protocol was approved by the institutional review board at each participating center.

#### Study Design

In this 12-month randomized, double-blind, placebo-controlled, multicenter study, the patients were stratified according

From the Department of Medicine, St. Joseph's Hospital, McMaster University, Hamilton, Ont. (J.D.A., W.G.B.); the Centre Hospitalier de l'Université Laval, Ste.-Foy, Que. (J.B.); Foothills Hospital, University of Calgary, Calgary, Alta. (D.H.); St. Joseph's Hospital and Victoria General Hospital, University of Western Ontario, London (A.H.); St. Michael's Hospital and Toronto General Hospital, University of Toronto, Toronto (R.J.); Vancouver General Hospital, University of British Columbia, Vancouver (D.L.K., B.L.); St. Paul's Hospital, University of Saskatchewan, Saskatoon (W.O.); Hôpital Saint-Luc, Université de Montréal, Montreal (L.-G.S.); and Montreal General Hospital, McGill University, Montreal (A.T.) — all in Canada; and Procter & Gamble Pharmaceuticals, Cincinnati (A.A.C.). Address reprint requests to Dr. Adachi at 501-25 Charlton Ave. E., Hamilton, ON L8N 1Y2, Canada.

Other authors were Algis Jovaisas, M.D. (Ottawa General Hospital, University of Ottawa, Ottawa, Ont.), William C. Sturtridge, M.D. (St. Michael's Hospital and Toronto General Hospital, University of Toronto, Toronto), Tassos P. Anastasiades, M.D. (St. Mary's of the Lake Hospital, Queen's University, Kingston, Ont.), John G. Hanly, M.D. (Victoria General Hospital, Dalhousie University, Halifax, N.S.), Janet E. Pope, M.D. (Victoria General Hospital, University of Western Ontario, London), and Reginald Dias, B.Sc., Zebulun D. Horowitz, M.D., and Simon Pack, Ph.D. (Procter & Gamble Pharmaceuticals, Cincinnati).

**TABLE 1. BASE-LINE CHARACTERISTICS OF THE PATIENTS IN THE ETIDRONATE AND PLACEBO GROUPS.\***

CHARACTERISTIC	ETIDRONATE (N=67)	PLACEBO (N=74)
Age — yr		
Mean	62±14	60±16
Range	31–83	19–87
Men — no. (%)	26 (39)	28 (38)
Women — no. (%)	41 (61)	46 (62)
Premenopausal	8 (20)	9 (20)
Postmenopausal	33 (80)	37 (80)
Mean dose of prednisone or equivalent — mg/day	21±22	23±22
Bone density of lumbar spine — g/cm <sup>2</sup>		
Men	0.94±0.14	0.90±0.18
Premenopausal women	0.98±0.14	1.00±0.17
Postmenopausal women	1.03±0.11	1.01±0.12
Postmenopausal women	0.90±0.13	0.81±0.14
Vertebral fractures — no. of patients (%)	30 (45)	36 (49)
Serum 25-hydroxyvitamin D — ng/ml	31±10	30±10
Serum parathyroid hormone — pg/ml	36±15	35±20
Underlying disease requiring corticosteroids — no. of patients		
Ankylosing spondylitis	2	1
Chronic interstitial lung disease	2	3
Dermatomyositis	2	1
Skin disease	0	2
Chronic active hepatitis	2	6
Systemic lupus erythematosus	5	2
Myasthenia gravis	1	2
Polymyositis	4	2
Polymyalgia rheumatica	28	25
Rheumatoid arthritis	13	21
Temporal arteritis	6	4
Vasculitis	2	5

\*Plus-minus values are means ±SD. To convert values for 25-hydroxyvitamin D to nanomoles per liter, multiply by 2.5; to convert values for parathyroid hormone to picomoles per liter, multiply by 0.105. The normal reference range for 25-hydroxyvitamin D is 8 to 52 ng per milliliter, and for serum parathyroid hormone, 10 to 65 pg per milliliter.

to sex and menopausal status: men, premenopausal women, and postmenopausal women. All the patients were subsequently randomly assigned to receive one tablet of either etidronate disodium (400 mg; Didronel, Procter & Gamble Pharmaceuticals, Cincinnati) or placebo per day for 14 days, followed in all patients by 76 days of calcium carbonate (500 mg of elemental calcium; Didrocal, Procter & Gamble Pharmaceuticals). This cycle was repeated three times during the one-year treatment period. The patients were instructed to take the study drug with water at least two hours before or after a meal and to take the calcium carbonate at bedtime.<sup>8,9</sup>

Disease activity was measured by the Ritchie Articular Index<sup>10</sup> in the patients with rheumatoid arthritis and on the basis of the erythrocyte sedimentation rate in those with polymyalgia rheumatica. Height was measured primarily with a stadiometer; one site used a pull-out height ruler on the weight scale. Height and weight were measured at base line and at weeks 26 and 52. Serum and urine samples were collected at base line and at weeks 26 and 52 for measurements of biochemical markers of bone resorption and formation. The serum and urine samples were collected in the morning (8 to 11 a.m.) after an overnight fast. Bone-specific alkaline phosphatase was measured in serum by an immunoradiometric assay (Hybritech, San Diego, Calif.), and N-telopeptide of type I collagen was measured in urine by an enzyme-linked immunosorbent assay (Ostex International, Seattle).

**Bone-Mass and Radiologic Measurements**

The primary outcome was the difference between the two treatment groups at week 52 in the mean percent change from base line in the bone density of the lumbar spine (L1 to L4). Secondary measures included changes in the bone density of the proximal femur (neck and trochanter) and distal and midshaft (one third of the way up) radius.

All measurements of bone mass were made by dual-energy x-ray absorptiometry. Scans of the lumbar spine were obtained twice at base line and at 52 weeks and once at 26 weeks; hip scans were obtained twice at base line and once at 26 and 52 weeks. The average of the values of the duplicate scans was used in the analysis.

The Hologic spine and linearity phantom (a calibration standard) was scanned on each instrument before the study began and after it was completed to establish instrument cross-calibration values. Quality-assurance data were collected daily from each center to assess the performance of the scanners.

Lateral and anteroposterior x-ray films of the spine were obtained at base line, and an x-ray film of the lateral spine was also obtained at week 52. After all the patients had completed the study, the films were evaluated by an experienced skeletal radiologist who was unaware of the patients' identity, treatment, and dates of examination. The vertebral-deformity score<sup>11</sup> was determined by grading each vertebral body (T4 to L4) according to the following criteria: grade 0, normal; grade 1, a 20 to 25 percent reduction in the height of the anterior, middle, or posterior dimension of the vertebral body in comparison with the adjacent vertebrae; grade 2, a 26 to 40 percent reduction; and grade 3, a reduction greater than 40 percent. A new vertebral fracture was defined as any increase in the vertebral-deformity score from base line. A spinal-deformity index was also calculated for each patient by adding the individual vertebral-deformity scores and dividing by the number of vertebrae evaluated.<sup>11</sup>

**Statistical Analysis**

An intention-to-treat analysis was performed. Analysis of covariance was performed to test for differences between groups in the mean percent change from base line to weeks 26 and 52 in bone density. The two covariates were the mean daily corticosteroid dose and a binary variable indicating the extent of corticosteroid therapy received within the 100 days before study entry. Each of the three subgroups — men, premenopausal women, and postmenopausal women — were analyzed separately. One-way analysis of variance was performed to test for treatment differences within subgroups in bone density and to test for differences between treatment groups in markers of bone formation and resorption. The Wilcoxon rank-sum test was used to test for differences between groups in the corticosteroid dose at base line, week 26, and week 52. Fisher's exact test was used to determine differences between groups in the rates of response to treatment at week 52 and to compare the proportion of patients with new vertebral fractures in each group. A two-sample t-test was used to test for differences in the number of new vertebral fractures per patient and to determine differences between groups in the change in the spinal-deformity index between base line and week 52; probability levels were determined with a permutation test. Values are given as means (±SE) unless otherwise indicated.

**RESULTS**

A total of 141 patients were enrolled at base line: 67 were randomly assigned to receive etidronate, and 74 were assigned to receive placebo. Twenty-four patients withdrew before the study was completed. One patient in the placebo group and four in the etidronate group withdrew because of adverse events. Only one withdrawal in the etidronate group was

**TABLE 2.** MEAN CHANGE BETWEEN BASE LINE AND WEEK 52 IN THE BONE DENSITY OF THE LUMBAR SPINE, TROCHANTER, FEMORAL NECK, DISTAL RADIUS, AND MIDSHAFT RADIUS, ACCORDING TO SEX AND MENOPAUSAL STATUS.\*

VARIABLE	ETIDRONATE		PLACEBO		P VALUE†
	% CHANGE	NO. OF PATIENTS‡	% CHANGE	NO. OF PATIENTS‡	
Lumbar spine					
Men	-0.12±0.73	18	-2.62±1.03	23	0.07
Premenopausal women	-0.10±0.98	7	-4.57±1.22	8	0.02
Postmenopausal women	1.23±0.87	29	-3.33±0.87	31	0.001
Total	0.61±0.54	54	-3.23±0.60	62	0.02
Trochanter					
Men	0.69±0.78	17	-1.92±1.11	24	0.08
Premenopausal women	-0.85±2.07	7	-5.98±1.58	8	0.07
Postmenopausal women	2.48±0.99	29	-2.54±0.90	31	<0.001
Total	1.46±0.67	53	-2.74±0.66	63	0.02
Femoral neck					
Men	-0.49±1.09	17	-2.21±1.18	24	0.31
Premenopausal women	-1.63±1.25	7	-3.03±1.26	8	0.45
Postmenopausal women	1.03±1.01	29	-0.90±0.97	31	0.17
Total	0.19±0.68	53	-1.67±0.67	63	0.63
Distal radius					
Men	-0.76±0.85	18	1.34±1.27	24	0.21
Premenopausal women	2.63±1.64	7	3.28±2.06	8	0.81
Postmenopausal women	0.78±1.27	29	-1.32±1.69	31	0.33
Total	0.51±0.77	54	0.28±1.01	63	0.70
Midshaft radius					
Men	0.54±0.74	18	-0.11±0.53	24	0.47
Premenopausal women	0.80±1.36	7	2.05±0.73	8	0.42
Postmenopausal women	-0.35±0.60	29	-0.59±0.63	31	0.78
Total	0.10±0.44	54	-0.07±0.39	63	0.62

\*Plus-minus values are means ±SE.

†The P values were calculated with one-way analysis of variance.

‡The number of patients with analyzable data is shown.

considered to be drug related (the patient had an elevated serum creatinine level). One patient in the etidronate group in whom pneumonia developed died of respiratory failure during the study. Ten patients in the placebo group and eight in the etidronate group withdrew because of protocol violations.

The treatment groups were similar with respect to base-line characteristics (Table 1). The mean daily corticosteroid dose was similar in the groups at 26 and 52 weeks: 14±12 and 11±9 mg per day, respectively (cumulative dose, 4119±389 mg), in the placebo group and 13±10 and 11±8 mg per day, respectively (cumulative dose, 3911±385 mg), in the etidronate group. For the analysis of disease activity, only patients with polymyalgia rheumatica and rheumatoid arthritis were included, because of the small number of patients with other diseases. There was no difference in disease activity between groups at base line or at week 52.

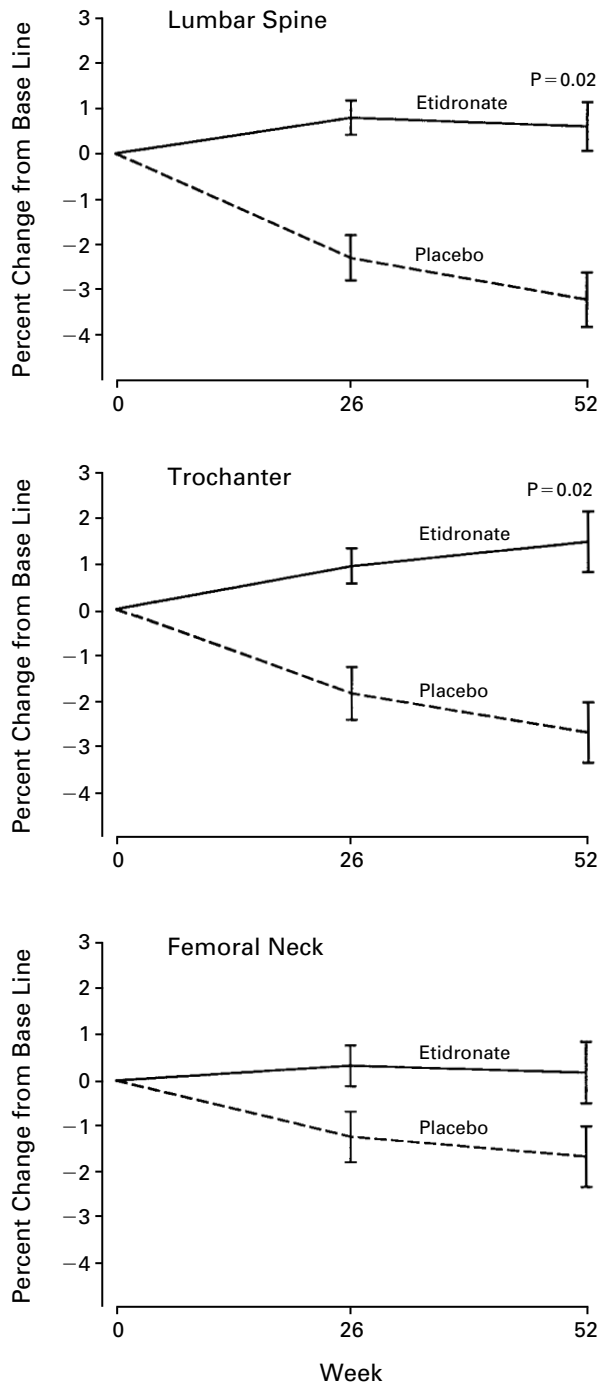
#### Measurements of Bone Mass

The bone density of the lumbar spine and trochanter did not change significantly in the etidronate group, whereas it declined in the placebo group,

as calculated by one-way analysis of variance (Table 2 and Fig. 1). The difference between treatment groups at week 52 (calculated by analysis of covariance) in the mean change from base line was 3.72±0.88 percentage points for the lumbar spine (P=0.02) and 4.14±0.94 percentage points for the trochanter (P=0.02). The mean difference between groups in the bone density of the femoral neck at week 52 was 1.88±1.07 (P=0.63) (Fig. 1). No significant differences between groups were found with respect to the bone density of the distal and midshaft radius (Table 2).

At 52 weeks, the decrease in the bone density of the lumbar spine was smaller in all three subgroups (men, premenopausal women, and postmenopausal women) of the etidronate group than in the placebo group, as estimated by one-way analysis of variance (Table 2). The mean difference between the two groups of the men was 2.50±1.34 percentage points (P=0.07). For premenopausal and postmenopausal women, the mean differences were 4.47±1.60 percentage points (P=0.02) and 4.56±1.24 percentage points (P=0.001), respectively.

The rates of response to treatment are shown in



**Figure 1.** Mean ( $\pm$ SE) Change in the Bone Density of the Lumbar Spine (Top Panel), Trochanter (Middle Panel), and Femoral Neck (Bottom Panel) between Base Line (Week 0) and Weeks 26 and 52 in the Etidronate and Placebo Groups. The P values indicate significant differences between treatment groups.

Table 3. A patient was considered to have had a response if the slope of the bone density of the spine was greater than zero, as determined by linear regression analysis (calculated with three measurements of bone density — base line, 26 weeks, and 52 weeks — in all but four patients, in whom two measurements were taken, one at base line and one at 26 weeks). More patients had a response in the etidronate group than in the placebo group (59 percent vs. 23 percent,  $P<0.001$ ).

**Fractures and Height**

Ten patients in the placebo group (15 percent) and five patients in the etidronate group (9 percent) had a total of 27 new vertebral fractures during the study (Table 4). One patient in each group had a fracture in a previously deformed vertebra, whereas the other patients had fractures in previously undeformed vertebrae. The relative risk of fractures in the etidronate group as compared with the placebo group was 0.6 (95 percent confidence interval, 0.2 to 1.6). The mean number of vertebral fractures per patient during the study was  $0.3\pm0.1$  in the placebo group and  $0.1\pm0.04$  in the etidronate group ( $P=0.09$ ). The mean change from base line in the spinal-deformity index was  $0.03\pm0.01$  in the placebo group and  $0.01\pm0.003$  in the etidronate group ( $P=0.09$ ).

Among the postmenopausal women, treatment with etidronate was associated with an 85 percent reduction in the proportion with vertebral fractures (1 of 31 women, vs. 7 of 32 women receiving placebo;  $P=0.05$ ). In addition, as compared with postmenopausal women who received placebo, postmenopausal women who received etidronate had fewer vertebral fractures per patient ( $P=0.04$ ) and a smaller mean change from base line in the spinal-deformity index ( $P=0.03$ ).

The proportion of patients who lost height during the study was lower in the etidronate group (28 percent, 15 of 54) than in the placebo group (51 percent, 32 of 63;  $P=0.01$ ). This difference was more pronounced in postmenopausal women, among whom 34 percent in the etidronate group (10 of 29) and 68 percent in the placebo group (21 of 31) lost height ( $P=0.02$ ).

**Markers of Bone Turnover**

The base-line values for serum and urine markers of bone turnover were similar in the two treatment groups (data not shown). In the etidronate group, the serum bone-specific alkaline phosphatase concentration had decreased  $17.6\pm4.2$  percent by week 26 ( $P<0.001$ ) and  $7.9\pm5.3$  percent by week 52 ( $P=0.15$ ). The difference between treatment groups at week 52 was not significant ( $P=0.09$ ). Urinary N-telopeptide excretion had decreased  $44.8\pm5.3$  percent by week 26 ( $P<0.001$ ) and  $52.5\pm4.9$  percent by week 52 ( $P<0.001$ ) in the etidronate group.

The difference between treatment groups was significant ( $P < 0.001$ ).

### Safety

Eight patients in the placebo group had a total of 18 adverse events that were considered to be causally related to treatment, as did eight patients in the etidronate group, who had a total of 9 adverse events. Most of the adverse events were gastrointestinal in origin and were mild, transient, and similar in frequency in the two groups (affecting 12 of 74 patients in the placebo group [16 percent] and 13 of 67 in the etidronate group [19 percent]). The gastrointestinal side effects were abdominal pain, diarrhea, constipation, heartburn, and dyspepsia, and none of the patients withdrew as a consequence.

### DISCUSSION

In our randomized, controlled study, we found that one year of treatment with etidronate and calcium prevented bone loss and vertebral fractures in patients with a variety of disorders who were taking corticosteroids. Several previous nonrandomized studies have also suggested that therapy with etidronate prevented bone loss in patients treated with corticosteroids.<sup>6,7,12-14</sup>

Fractures are common in patients who take corticosteroids for long periods. In this study, treatment with etidronate was associated with a 40 percent reduction in the proportion of patients who sustained new vertebral fractures. The beneficial effect of etidronate on the incidence of fracture was also evidenced by the lower number of fractures per patient, the lower number of new vertebral deformities, and the preservation of height, although the differences from placebo were not statistically significant.

Because the effect of etidronate on corticosteroid-induced bone loss may be influenced by risk factors for osteoporosis, the study patients were stratified according to sex and menopausal status. The postmenopausal women were older and had the lowest bone density of the lumbar spine at base line. In these women, etidronate therapy was associated with a substantial reduction in the number of new vertebral fractures. In addition, there was a significant reduction in the fracture rate and in the mean change from base line in the spinal-deformity index. It is therefore reasonable to conclude that etidronate therapy had a protective effect with respect to the fracture rate in corticosteroid-treated postmenopausal women. Other therapies, such as calcium, vitamin D preparations, and calcitonin, have been studied prospectively and have prevented bone loss predominantly in the lumbar spine.<sup>15,16</sup> None, however, have reduced the fracture rate.

Overall, etidronate therapy was well tolerated in this diverse group of corticosteroid-treated patients. The number of adverse events and number of pa-

**TABLE 3. RATES OF RESPONSE TO TREATMENT WITH ETIDRONATE OR PLACEBO.\***

GROUP	ETIDRONATE	PLACEBO	P VALUE†
Men	11/20 (55)	5/23 (22)	0.03
Premenopausal women	3/7 (43)	0/8	0.08
Postmenopausal women	19/29 (66)	10/33 (30)	0.01
Total	33/56 (59)	15/64 (23)	<0.001

\*The values shown are the numbers of patients responding over the numbers of patients with analyzable data, with percentages given in parentheses. A patient was considered to have had a response to therapy if the slope (percent change per year) of the bone density of the spine was greater than zero, as determined by linear regression analysis.

†Fisher's exact test was used to calculate the P values.

**TABLE 4. INCIDENCE OF VERTEBRAL FRACTURES AMONG CORTICOSTEROID-TREATED PATIENTS WHO WERE GIVEN ETIDRONATE OR PLACEBO.\***

VARIABLE	ETIDRONATE	PLACEBO
No. of patients with new vertebral fractures	5/57	10/65
Men	4/19	3/25
Premenopausal women	0/7	0/8
Postmenopausal women	1/31	7/32
Total no. of vertebrae fractured	5	22
No. of patients with multiple vertebral fractures	0	6
Total no. of nonvertebral fractures	3	8†

\*The values shown are the numbers of patients with new vertebral fractures over the numbers of patients with analyzable data.

†Some patients in the placebo group had more than one nonvertebral fracture.

tients who dropped out because of these adverse events were similar in the two treatment groups.

Our study is not without limitations, and the results should be interpreted in the context of its design. We do not know whether the protective effect of etidronate therapy on bone density and the reduction in fracture rate are sustained beyond one year. Since a large proportion of the patients had polymyalgia rheumatica or rheumatoid arthritis, our results should be applied with caution to many other diseases for which corticosteroids are used. Although bone biopsies were not performed, measurements of bone-specific alkaline phosphatase, a sensitive marker of bone formation,<sup>17</sup> showed an initial reduction and then a recovery at 52 weeks. Moreover, urinary *N*-telopeptide, a sensitive marker of bone resorption, had decreased by 52.5 percent at 52 weeks in the etidronate group, a value that is very similar to the value that was recently reported in postmenopausal women receiving hormone-replacement

treatment.<sup>18</sup> This suggests that etidronate therapy is safe in corticosteroid-treated patients.

We conclude that intermittent administration of etidronate is a safe therapy for preventing corticosteroid-induced osteoporosis in patients with a wide range of underlying disorders.

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