

## INTRAVENOUS ZOLEDRONIC ACID IN POSTMENOPAUSAL WOMEN WITH LOW BONE MINERAL DENSITY

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### ABSTRACT

**Background** Bisphosphonates are effective agents for the management of osteoporosis. Their low bioavailability and low potency necessitate frequent administration on an empty stomach, which may reduce compliance. Gastrointestinal intolerance limits maximal dosing. Although intermittent intravenous treatments have been used, the optimal doses and dosing interval have not been systematically explored.

**Methods** We studied the effects of five regimens of zoledronic acid, the most potent bisphosphonate, on bone turnover and density in 351 postmenopausal women with low bone mineral density in a one-year, randomized, double-blind, placebo-controlled trial. Women received placebo or intravenous zoledronic acid in doses of 0.25 mg, 0.5 mg, or 1 mg at three-month intervals. In addition, one group received a total annual dose of 4 mg as a single dose, and another received two doses of 2 mg each, six months apart. Lumbar-spine bone mineral density was the primary end point.

**Results** There were similar increases in bone mineral density in all the zoledronic acid groups to values for the spine that were 4.3 to 5.1 percent higher than those in the placebo group ( $P < 0.001$ ) and values for the femoral neck that were 3.1 to 3.5 percent higher than those in the placebo group ( $P < 0.001$ ). Biochemical markers of bone resorption were significantly suppressed throughout the study in all zoledronic acid groups. Myalgia and pyrexia occurred more commonly in the zoledronic acid groups, but treatment-related dropout rates were similar to that in the placebo group.

**Conclusions** Zoledronic acid infusions given at intervals of up to one year produce effects on bone turnover and bone density as great as those achieved with daily oral dosing with bisphosphonates with proven efficacy against fractures, suggesting that an annual infusion of zoledronic acid might be an effective treatment for postmenopausal osteoporosis. (N Engl J Med 2002;346:653-61.)

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ORAL bisphosphonates are widely used for treating osteoporosis and have been shown to increase bone mineral density and decrease the rate of fracture.<sup>1,2</sup> However, they do have limitations related to long-term compliance, gastrointestinal intolerance, and poor and variable absorption from the gastrointestinal tract. Intermittent intravenous administration of bisphosphonates might address some of these problems and has been shown to be effective in the treatment of malignant hypercalcemia and Paget's disease and to reduce the rate of skeletal complications in patients with breast carcinoma or multiple myeloma. Evidence suggests that intravenous bisphosphonates increase bone mineral density in patients with osteoporosis, but most relevant studies have been small, unblinded, and short-term and have not systematically examined the effects of the dose and dosing interval on changes in bone mineral density and markers of bone turnover.<sup>3-6</sup>

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Zoledronic acid is the most potent bisphosphonate that has been studied in clinical trials to date.<sup>7</sup> It is superior to pamidronate in the treatment of cancer-related hypercalcemia.<sup>8</sup> Because it has high potency, only small doses are required for the inhibition of bone resorption, and long dosing intervals may be used. We undertook a phase 2 study to examine the effect of intravenous zoledronic acid on bone density and bone turnover in postmenopausal women with low bone density and to assess the effects of varying the total dose administered and the dosing interval.

## METHODS

### Study Subjects

A total of 351 postmenopausal women 45 to 80 years of age were studied at 24 centers in 10 countries. In all the women, menopause had occurred at least five years previously, either naturally or as the result of bilateral oophorectomy. All women had a bone mineral density at the lumbar spine (L1 to L4) that was at least 2.0 SD below the mean value for young adults (a T score lower than -2) and had no more than one vertebral fracture at screening. The date of onset of menopause was defined as the date of oophorectomy when applicable or as 12 months after the cessation of menses in women over 50 years of age and 18 months after the cessation of menses in women between 45 and 49 years of age. Major criteria for exclusion included systemic estrogen treatment within the previous three months, evidence of secondary osteoporosis, clinical or laboratory evidence of hepatic or renal disease, disorders of the parathyroid or thyroid glands, a serum 25-hydroxyvitamin D concentration of 15 ng per milliliter (37 nmol per liter) or less, a history of cancer, previous treatment with bisphosphonates or fluoride, and current therapy with any other drug known to affect the skeleton. The protocol was approved by the ethics committee at each center, and all the women gave written informed consent. Thirty-five women withdrew from the study, most commonly for personal reasons (in the case of 15 women) or because of adverse events (14 women). Thus, 316 women completed the study.

### Treatment

All women received a calcium supplement (1 g per day). At study entry the women were randomly assigned to receive one of six treatment regimens in a double-blind fashion. Three groups received zoledronic acid by intravenous infusion every three months, one group at a dose of 0.25 mg, one at a dose of 0.5 mg, and one at a dose of 1 mg. Two other groups received a total dose of 4 mg of zoledronic acid — one group receiving a single 4-mg infusion at the beginning of the trial and the other group receiving two doses of 2 mg each, one at base line and the other at six months. Thus, there were three groups that received a total dose of 4 mg in one year. The sixth group received only placebo (saline). To maintain blinding, all women received an intravenous infusion of either zoledronic acid or placebo every three months. All infusions were 20 ml in volume and were infused over a period of five minutes. A dose of 4 mg given in this way produces a mean ( $\pm$ SD) peak serum concentration of zoledronic acid of  $393 \pm 100$  ng per milliliter. Infusions were prepared at each center by a pharmacist who had no contact with the patients and were labeled with the subject's study number and supplied to the study personnel.

### Bone Density Measurement

The bone mineral density of the lumbar spine, the nondominant proximal femur and forearm, and the total body were measured by dual-energy x-ray absorptiometry at base line and at 6, 9, and 12 months with the use of Hologic QDR (Hologic, Waltham, Mass.) or Lunar (Madison, Wis.) instruments. Data were converted

to Hologic-equivalent values by the method of Hui et al.<sup>9</sup> A central laboratory (Institut für Funktionsanalyse, Hamburg, Germany) was responsible for the supervision of quality control for these measurements and notified investigators if any patient had a decrease in bone density of more than 5 percent from the base-line values.

### Markers of Bone Turnover

Measurement of biochemical markers was performed in a central laboratory with the use of established methods. For serum bone-specific alkaline phosphatase, the Tandem-MP Ostase assay was used (Hybritech, Liege, Belgium). Serum osteocalcin was measured with the N-MID one-step enzyme-linked immunosorbent assay (Osteometer, Herlev, Denmark). Urinary type I collagen cross-linked N-telopeptide was measured with the Osteomark assay (Ostex, Seattle). Serum type I collagen C-telopeptide was measured with the CrossLaps assay (Osteometer).

### Statistical Analysis

The necessary sample size was calculated as the number of patients needed to detect a difference between the zoledronic acid groups and the placebo group of at least 4 percent in the degree of change in lumbar-spine bone mineral density from base line to 12 months. Bonferroni's correction was used to adjust for multiple comparisons in order to ensure an overall nominal significance level of 0.05. Given a noncentral t distribution with a type I error of 0.025, a power of 80 percent, a two-sided alternative, and a standard deviation of 5.7 percent, we calculated that 40 patients were needed in each treatment group in order to allow detection of a difference of 4 percent. To allow for a possible 15 percent dropout rate, a total sample size of 290 was selected.

All analyses were performed according to the intention-to-treat principle with the use of all available data from all patients who received study drug. Missing values were not imputed or replaced. Analysis of covariance was performed (with the Proc Mixed procedure of SAS software [SAS Institute, Cary, N.C.]) to estimate differences between the treatment groups. The statistical fixed-effects model considered center and treatment as main variables. In addition, the base-line values, if measured, were used as covariates. The analyses were repeated with the last observation carried forward and produced essentially the same results (data not shown).

For the primary variable, adjustment for multiple comparisons between placebo and the active doses of zoledronic acid was performed at a one-sided alpha level of 0.025, according to the method of Marcus et al.<sup>10</sup> For secondary variables, pairwise comparisons were investigated in the exploratory analysis (unadjusted for multiple comparisons). The pairwise comparisons were tested at a two-sided level of significance of 0.05. In addition to the P value for the comparisons between treatment groups, estimates of the differences and associated 95 percent confidence intervals were calculated.

The protocol was designed and developed by the sponsor and submitted to the investigators for comments and amendments. The final protocol was then accepted by the investigators and submitted to the ethics review committees of their institutions for approval. Data management and statistical analysis were performed by the sponsor. Interpretation of the data and preparation of the manuscript were performed by a publication committee that included three academic researchers who were investigators in the trial (Drs. Reid, Brown, and Burckhardt) and Dr. Trechsel, the author of the study protocol, as a representative of the sponsor. These authors had full and unfettered access to the data and take full responsibility for the completeness and accuracy of the reported data. The study sponsor placed no limits on statements made in the final paper.

## RESULTS

### Study Subjects

The base-line characteristics of the women who participated in the study are summarized in Table 1.

All but two women were white, and none had vertebral fractures at study entry.

**Bone Mineral Density**

Mean bone-mineral-density values in the lumbar spine corresponded to a T score of -2.9. All groups receiving zoledronic acid regimens had a progressive increase in bone mineral density in the lumbar spine throughout the 12-month study period, although the rate of increase tended to slow in the second half of the study (Fig. 1A). Throughout the study, the values for lumbar-spine bone mineral density achieved with all zoledronic acid regimens were significantly higher than those in the placebo group ( $P < 0.001$ ), and there were no significant differences among the zoledronic acid groups. At 12 months, the mean lumbar-spine bone mineral density in the groups receiving zoledronic acid was 4.3 to 5.1 percent higher than the mean value in the placebo group, which remained stable. The bone mineral density in the femoral neck also increased progressively throughout the study period; all zoledronic acid groups had similar increases to values that were significantly higher than those in the placebo group (differences of 3.1 to 3.5 percent at 12 months,  $P < 0.001$ ) (Fig. 1B). The femoral-neck bone mineral density declined by 0.4 percent in the placebo group.

Bone mineral density at the distal radius responded to zoledronic acid treatment to a lesser extent, re-

sulting in differences from the placebo group of 0.8 to 1.6 percent at 12 months (data not shown); in the placebo group, distal radial bone mineral density decreased by 0.8 percent. All zoledronic acid regimens except the four doses of 0.25 mg each resulted in distal radial bone mineral density that was significantly greater than that in the placebo group ( $P \leq 0.05$  for all comparisons). The results for total-body bone mineral density were similar (data not shown). At 12 months, the differences in total-body bone mineral density between the zoledronic acid groups and the placebo group ranged from 0.9 percent to 1.3 percent and were significant ( $P < 0.03$  for all comparisons) for all regimens except the four doses of 0.5 mg each.

**Markers of Bone Turnover**

Markers of bone resorption reached a nadir at one month (median decreases of 65 to 83 percent in serum C-telopeptide and 50 to 69 percent in the urinary N-telopeptide:creatinine ratio), whereas there were no significant changes in the placebo group (Fig. 2). The decrease in markers of resorption tended to be dose-dependent, particularly at three months — a pattern that is consistent with previous reports that higher doses of bisphosphonates increase the duration of action of the drug.<sup>11</sup> We do not have full documentation of the immediate reductions in bone resorption after each infusion, because most samples were obtained only every three months. The suppression of

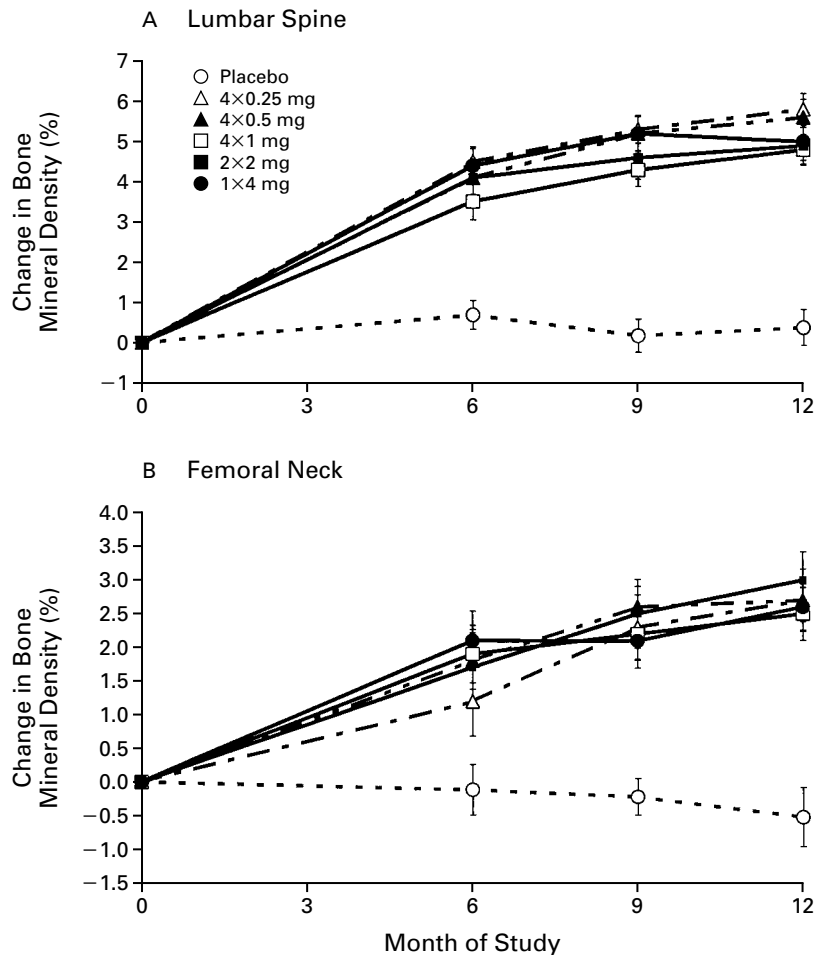
TABLE 1. BASE-LINE CHARACTERISTICS.\*

CHARACTERISTIC	ZOLEDRONIC ACID GROUPS					PLACEBO GROUP (N=59)
	4×0.25 mg (N=60)	4×0.5 mg (N=58)	4×1 mg (N=53)	2×2 mg (N=61)	1×4 mg (N=60)	
No. of women completing the study	51	52	48	55	53	57
Age (yr)	64±6	64±7	65±7	63±7	65±7	64±6
Weight (kg)	60±10	62±10	61±9	63±13	62±11	63±10
Height (cm)	158±6	158±6	158±6	159±6	159±6	160±6
Urinary N-telopeptide:creatinine ratio†	48±32	56±43	45±21	46±27	48±24	45±26
Serum C-telopeptide (nmol/liter)	5.5±2.8	5.3±2.2	4.7±1.8	4.8±1.9	5.1±1.9	4.8±1.8
Serum bone-specific alkaline phosphatase (µg/liter)	17±8	18±6	15±5	15±5	15±6	16±7
Serum osteocalcin (µg/liter)	26±10	24±11	26±9	22±10	24±11	24±13
Bone mineral density (g/cm <sup>2</sup> )‡						
Lumbar spine	0.74±0.06	0.72±0.08	0.73±0.06	0.73±0.07	0.73±0.08	0.74±0.07
Femur	0.70±0.09	0.71±0.11	0.71±0.09	0.72±0.09	0.74±0.11	0.71±0.08
Radial	0.43±0.05	0.43±0.06	0.43±0.06	0.43±0.06	0.43±0.06	0.43±0.06
Total body	0.90±0.09	0.90±0.10	0.90±0.09	0.90±0.09	0.90±0.09	0.88±0.08

\*Plus-minus values are means ±SD.

†N-telopeptide was measured in nanomoles, and creatinine in millimoles.

‡Data have been converted to Hologic-equivalent values.



**Figure 1.** Effects of Various Regimens of Zoledronic Acid and Placebo on Bone Mineral Density in the Lumbar Spine (Panel A) and the Femoral Neck (Panel B) in Postmenopausal Women with Low Bone Mineral Density.

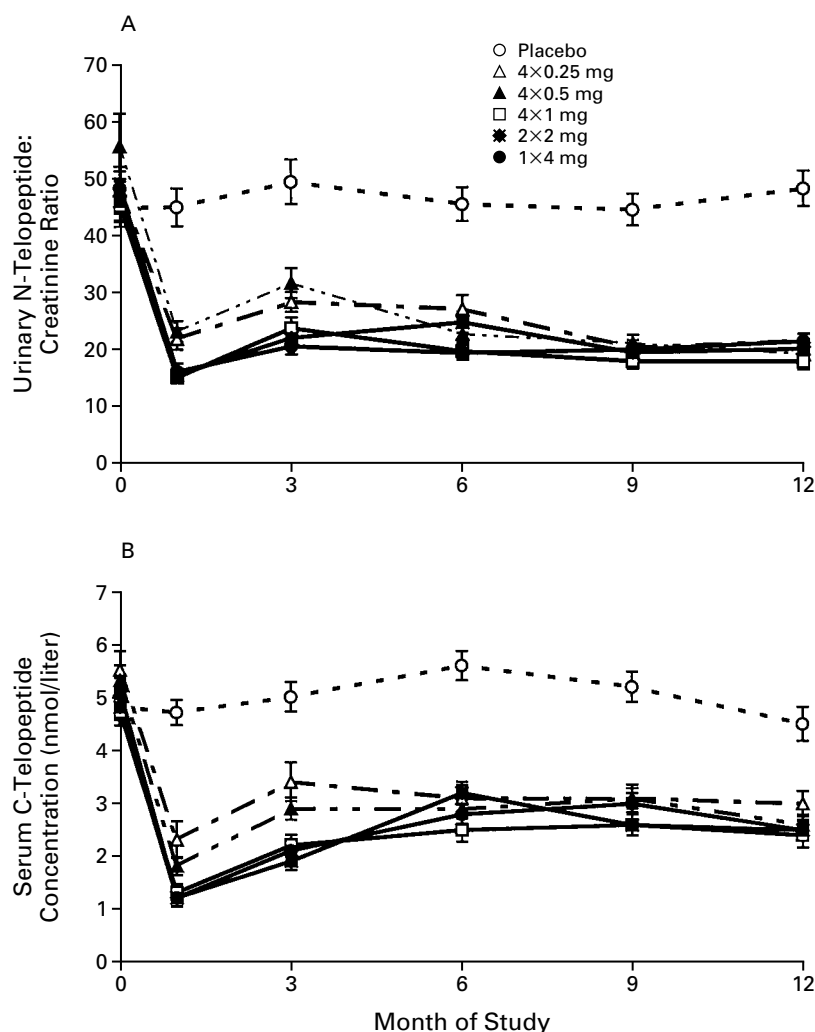
The curves show the mean changes from base line in the placebo group and the groups receiving zoledronic acid in four doses of 0.25 mg each, four doses of 0.5 mg each, four doses of 1 mg each, two doses of 2 mg each, and one dose of 4 mg. Achieved density with all regimens of zoledronic acid was significantly higher than that with placebo, and there were no significant differences among the zoledronic acid groups. I bars represent standard errors.

resorption was maintained at 12 months. At 12 months, the zoledronic acid regimens were associated with decreases of 49 to 52 percent in serum C-telopeptide (as compared with a decrease of 8 percent in the placebo group) and decreases of 54 to 65 percent in the ratio of urinary N-telopeptide to creatinine (as compared with an increase of 3 percent in the placebo group). All zoledronic acid groups had values for these markers of resorption that were significantly different from those in the placebo group ( $P < 0.01$  for all comparisons), but there were no significant differences among the zoledronic acid groups. Bone-specific alkaline phosphatase and osteocalcin,

which are serum markers of bone formation, showed similar responses, but there was no sharp decrease apparent at one month (Fig. 3). Again, suppression persisted at 12 months with all doses ( $P < 0.001$ ).

#### Bone Biopsies

A 7.5-mm transiliac biopsy specimen was obtained from 43 women and double-labeled with tetracycline. Of these specimens, 27 were complete and suitable for histomorphometric analysis. The sections were undecalcified and stained with Goldner's trichrome, except for tetracycline measurements, which were made on unstained sections. Women treated with zoledronic



**Figure 2.** Effects of Various Regimens of Zoledronic Acid and Placebo on Biochemical Markers of Bone Resorption.

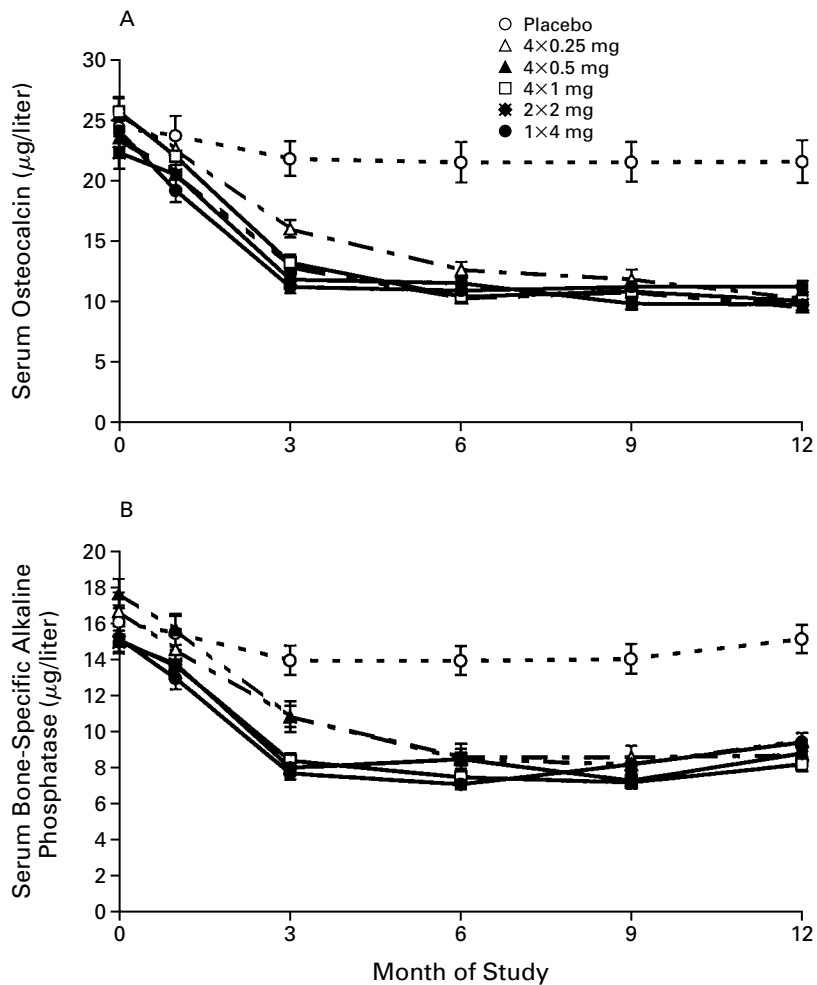
The ratio of N-telopeptide of type I collagen (in nanomoles) to creatinine (in millimoles) was measured in urine (Panel A). C-telopeptide was measured in serum (Panel B). The curves show the mean changes from base line in the placebo group and the groups receiving zoledronic acid in four doses of 0.25 mg each, four doses of 0.5 mg each, four doses of 1 mg each, two doses of 2 mg each, and one dose of 4 mg. Beginning at one month, the effects of all regimens were significantly different from those of placebo. The I bars represent standard errors.

acid at any dose had significantly lower proportions of mineralizing surfaces, rates of bone formation, adjusted mineral apposition rates, and activation frequencies than the women in the placebo group (differences of 71 percent to 84 percent,  $P < 0.05$ ); there were non-significant differences in the proportion of eroded surface (39 percent lower than that in the placebo group,  $P < 0.06$ ) and in eroded volume (48 percent lower,  $P < 0.07$ ). No change was noted in cortical bone thickness or porosity; cancellous bone volume; trabecular thickness, separation, or number; wall width of trabecular

bone packets; number of nodes per volume of tissue; or osteoid maturation time. No dose effect was found with respect to any of these factors. No evidence of osteomalacia was found, either by qualitative assessment or on the basis of such quantitative measures as osteoid thickness and volume or the mineral apposition rate. No other qualitative abnormalities were apparent.

#### Fractures

Spinal radiographs at base line and one year showed no vertebral fractures during the study. No nonver-



**Figure 3.** Effects of Various Regimens of Zoledronic Acid and Placebo on Serum Markers of Bone Formation.

The curves show the mean changes from base line in serum osteocalcin (Panel A) and serum bone-specific alkaline phosphatase (Panel B) in the placebo group and the groups receiving zoledronic acid in four doses of 0.25 mg each, four doses of 0.5 mg each, four doses of 1 mg each, two doses of 2 mg each, and one dose of 4 mg. Beginning at three months, the serum concentrations with all regimens of zoledronic acid were significantly lower than base-line values. The I bars represent standard errors.

tebral fractures occurred in the group receiving four doses of 0.25 mg of zoledronic acid; two nonvertebral fractures occurred in the group receiving four doses of 1 mg of zoledronic acid; and one nonvertebral fracture occurred in each of the other groups.

#### Safety

Mean serum calcium concentrations in the zoledronic acid groups declined significantly ( $P < 0.05$  for all comparisons), by approximately 0.08 mmol per liter, between base line and one month but were similar to those in the placebo group from three months

onward. Serum phosphate concentrations in the zoledronic acid groups had decreased by 0.06 to 0.12 mmol per liter at one month and generally remained about 0.05 mmol per liter below those in the placebo group throughout the study period, although they did not differ significantly from those in the placebo group at one year. Intact parathyroid hormone was measured in serum at base line and 12 months. There were no significant differences among the groups at the 12-month follow-up, although the mean value was about 30 percent higher than the base-line value in the women in the group receiving four doses of 1 mg of zole-

dronic acid, possibly because sampling was performed only three months after the last dose had been administered in this group.

The rates of adverse events were similar in all the active-treatment groups (Table 2). However, treatment-related adverse events were significantly more common in the zoledronic acid groups than in the placebo group (rates of 45 to 67 percent vs. 27 percent; data not shown). In the zoledronic acid groups, most adverse events were instances of musculoskeletal pain, nausea, or fever, most of which were rated as mild. Most occurred the first time the drug was administered. Five women withdrew from the study because of drug-related adverse events, all of which were reactions after the first infusion of zoledronic acid. These withdrawals were not dose-related; two occurred in women who were receiving the lowest dose and two in women receiving the highest dose. There was no evidence of adverse effects on renal function with any of these regimens. Overall, the proportions of women who withdrew from the study because of adverse events were similar in all groups. Symptoms at the infusion site were uncommon in all groups (e.g., reported in no patients receiving a single 4-mg dose of zoledronic acid and in two patients receiving placebo). Iritis did not develop in any patients, and the occurrence of any eye disorder was uncommon (e.g., reported in two patients receiving a single 4-mg dose of zoledronic acid and in nine patients receiving placebo).

DISCUSSION

Intermittent intravenous administration of the potent bisphosphonate zoledronic acid results in changes in biochemical markers of bone turnover and in bone mineral density that are similar to those observed

with daily oral bisphosphonate therapy. Thus, the reductions in markers at one year in the present study are similar to those seen with 5 mg of risedronate per day,<sup>12</sup> 2.5 to 5 mg of ibandronate per day,<sup>13</sup> and 10 mg of alendronate per day.<sup>14-16</sup> Zoledronic acid increases spinal bone mineral density at 12 months to 5 percent above values found in patients receiving placebo — an increase similar to that achieved with a daily 10-mg dose of alendronate (5 percent),<sup>17</sup> a daily 5-mg dose of risedronate (3 percent),<sup>12</sup> or a daily 150-mg dose of pamidronate (5 percent).<sup>18</sup> Intravenous zoledronic acid also produced results similar to those of the oral regimens at the femoral neck (alendronate, 3 percent increase in bone density; risedronate, 2 percent; pamidronate, 3 percent) and in the total body (alendronate, 1.5 percent increase; pamidronate, 1 percent).

Our study assessed longer intervals between doses than have been assessed by previous studies of intermittent bisphosphonate therapy. Etidronate has been used for many years in two-week oral courses administered at three-month intervals.<sup>19,20</sup> There is also evidence that intravenous pamidronate<sup>3</sup> or ibandronate,<sup>4</sup> given every three months, has beneficial effects on bone density in women with postmenopausal osteoporosis. The disappointing data on fractures from a recent study of intermittent ibandronate therapy (1 mg intravenously every three months)<sup>21</sup> has been interpreted as indicating that a dosing interval of three months is too long. However, this ibandronate regimen did not stably suppress markers of bone resorption; a substantial maximal suppression of C-telopeptide excretion (by 50 percent) was rapidly offset, so that the level before the next dose was only 10 to 20 percent below that in the placebo group.<sup>4</sup> As a result, the changes in bone density (increases of 2.9 percent

TABLE 2. ADVERSE EVENTS.\*

VARIABLE	ZOLEDRONIC ACID GROUPS					PLACEBO GROUP (N=59)
	4×0.25 mg (N=60)	4×0.5 mg (N=58)	4×1 mg (N=53)	2×2 mg (N=61)	1×4 mg (N=60)	
Adverse events — no.	236	236	255	271	269	210
Women with an adverse event — no. (%)						
Any	52 (87)	50 (86)	50 (94)	56 (92)	54 (90)	45 (76)
Myalgia	12 (20)	6 (10)	7 (13)	10 (16)	6 (10)	1 (2)
Pyrexia	6 (10)	5 (9)	7 (13)	12 (20)	9 (15)	2 (3)
Arthralgia	9 (15)	8 (14)	9 (17)	15 (25)	5 (8)	9 (15)
Influenza-like illness	1 (2)	4 (7)	2 (4)	10 (16)	9 (15)	4 (7)
Nausea	3 (5)	4 (7)	5 (9)	6 (10)	8 (13)	3 (5)
Any leading to withdrawal from study	4 (7)	2 (3)	2 (4)	2 (3)	3 (5)	1 (2)
Any serious	4 (7)	4 (7)	7 (13)	5 (8)	6 (10)	3 (5)

\*Data are for all adverse events in each category, not just those classified as drug-related.

in the spine at 12 months<sup>4</sup> or to 4 percent higher than the spinal bone mineral density in the placebo group at 3 years<sup>21</sup>) were smaller than those found in our study; this effect is consistent with the moderate effect of this dose of ibandronate on the incidence of vertebral fracture (a 26 percent reduction at 3 years). Our data indicate that much longer dosing intervals are compatible with efficacy (in terms of both suppression of bone turnover and increase in bone density) if the dose of bisphosphonate is sufficiently large. Indeed, the present study does not establish a maximal dosing interval, since turnover remained suppressed at 12 months. Thus, it is possible that a longer interval between doses could be effective, particularly if larger doses of zoledronic acid were used.

How a single infusion of zoledronic acid suppresses bone turnover for so long remains to be determined. Prolonged suppression is not the result of the persistence of the drug in the circulation, given that by 24 hours after administration, drug levels are less than 1 percent of the postadministration peak and 40 percent of the dose has been excreted in the urine. The balance of the dose is presumably bound to bone and is slowly released back into the circulation, giving rise to a 167-hour terminal half-life in plasma. It has been thought that bisphosphonates are located exclusively on osteoclastic surfaces<sup>22</sup> and that short-term exposure inhibits activity in a single generation of basic multicellular units in bone. The life span of the basic multicellular unit (about three months) then determines the duration of action of the drug. However, evidence suggests that bisphosphonates are also deposited on osteoblastic and resting bone surfaces and remain there for the long term.<sup>23</sup> The existence of such deposits would provide a possible explanation for our results, since residue from a single dose could interfere with the future development of basic multicellular units at these surfaces. It is also possible that direct effects on existing basic multicellular units and osteocytes<sup>24,25</sup> result in reduced formation of succeeding basic multicellular units.

Zoledronic acid was generally well tolerated, and the rate of retention of subjects in the study was high. The adverse events that were more common in women receiving zoledronic acid are those that have occurred previously in patients receiving intravenous aminobisphosphonates and are transient. Infrequent doses may increase tolerance of these side effects.

The inclusion of a placebo group in this study permits quantification of the size of the therapeutic effect and facilitates comparison of the present data with those from other studies. We believe this use of a placebo is ethical, since the bone density used as a criterion for entry (a T score of less than -2) is higher than that required at the participating centers for a diagnosis of osteoporosis and would certainly not be consid-

ered to be a threshold for therapeutic intervention at these centers. Thus, the study was conducted in a low-risk population — a characterization supported by the fact that no spinal fractures occurred during the study period. Only one sixth of these low-risk subjects received placebo, and they received it for a maximum of 12 months, after which all women received active therapy.

Osteoporosis has been regarded as requiring daily therapy, and maintaining compliance with daily regimens for a predominantly asymptomatic condition has been a major problem.<sup>26,27</sup> Administration of treatment at intervals of 6 to 12 months or more is likely to be much more acceptable to patients and could reduce costs. A greater proportion of the at-risk population might take advantage of prophylaxis against osteoporosis if an intermittent regimen were used, and the rate of fractures might therefore decrease. However, studies that demonstrate an effect on the rate of fractures are needed before any recommendation can be made.

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