The Antiresorptive Effects of a Single Dose of Zoledronate Persist for Two Years: A Randomized, Placebo-Controlled Trial in Osteopenic Postmenopausal Women

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Context: Annual iv administration of 5 mg zoledronate decreases fracture risk. The optimal dosing interval of 5 mg zoledronate is not known.

Objective: Our objective was to determine the duration of antiresorptive action of a single 5-mg dose of iv zoledronate.

Design, Setting, and Participants: We conducted a double-blind, randomized, placebo-controlled trial over 2 yr at an academic research center, in a volunteer sample of 50 postmenopausal women with osteopenia.

Intervention: Intervention included 5 mg zoledronate.

Main Outcome Measures: Biochemical markers of bone turnover and bone mineral density of the lumbar spine, proximal femur, and total body.

Results: Compared with placebo, zoledronate treatment decreased mean levels of each of four markers of bone turnover by at least 38% (range 38–45%) for the duration of the study ($P < 0.0001$ for each marker). After 2 yr, bone mineral density was higher in the zoledronate group than the placebo group by an average of 5.7% (95% confidence interval = 4.0–7.4) at the lumbar spine, 3.9% (2.2–5.7) at the proximal femur, and 1.7% (0.8–2.5) at the total body ($P < 0.0001$ for each skeletal site). Between-groups differences in markers of bone turnover and bone mineral density were similar at 12 and 24 months. Mild secondary hyperparathyroidism was present throughout the study in the zoledronate group.

Conclusion: The antiresorptive effects of a single 5-mg dose of zoledronate are sustained for at least 2 yr. The magnitudes of the effects on markers of bone turnover and bone mineral density are comparable at 12 and 24 months. Administration of zoledronate at intervals of up to 2 yr may be associated with antifracture efficacy; clinical trials to investigate this possibility are justified. **(*J Clin Endocrinol Metab* 94: 538–544, 2009)**

Zoledronate is a potent nitrogen-containing bisphosphonate that, when administered as an annual 5-mg iv infusion, decreases the risk of fracture by 35–70% (depending upon the skeletal site) in osteoporotic men and women (1, 2) and decreases mortality by 28% after hip fracture (2). These results, together with the convenience of annual administration and a low rate of adverse effects, make it likely that zoledronate will be a widely used therapy for the treatment of osteoporosis for the foreseeable future.

At present, the duration of the antiresorptive action of an iv 5-mg dose of zoledronate is not known. In the phase II study of zoledronate, several iv dosing regimens, including a single 4-mg infusion administered at the baseline visit, were evaluated over a 12-month period (3). Twelve months after the 4-mg dose was

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

doi: 10.1210/jc.2008-2241 Received October 14, 2008. Accepted November 25, 2008.
First Published Online December 2, 2008

Abbreviations: BMD, Bone mineral density; CI, confidence interval; β-CTX, β-C-terminal telopeptide of type I collagen; MAR, mineral apposition rate; NTx, N-telopeptide of type 1 collagen; P1NP, procollagen type-I N-terminal propeptide.

administered, mean levels of bone resorption markers remained 50–60% below those in the group that received placebo. All subjects continuing in this study received further treatment with zoledronate at 12 months, so no data relating to the duration of effect of a single dose are available beyond 12 months (4). In the phase III study of zoledronate, annual dosing with 5 mg for 3 yr produced stable decreases in markers of bone turnover that ranged from 30–60% (1).

Recently, we reported that bone turnover markers remain stably decreased for up to 24 months after the second of two annual doses of 4 mg iv zoledronate in a placebo-controlled trial in HIV-infected men with osteopenia (5). These results suggest that the antiresorptive action of a 4-mg dose of iv zoledronate exceeds 12 months; it is plausible that the effects of the currently recommended dose of 5 mg may last even longer (6).

Determining the optimal dosing interval for iv zoledronate has important implications for patient care and pharmacoeconomics. In the present study, we set out to determine the duration of the antiresorptive action of a single dose of 5 mg iv zoledronate in postmenopausal women, the population in whom the drug is most likely to be used.

Subjects and Methods

Participants

Participants were women more than 5 yr postmenopausal, with bone mineral density (BMD) T score between −1 and −2 at either lumbar spine or total hip. Women who had illnesses or were receiving therapies that were known to affect the skeleton were ineligible, as were those with low bone mass (BMD T score at lumbar spine or total hip ≤ −2) or a previous hip or vertebral fracture, those who had ever used bisphosphonates, and those with any other major systemic disease.

Subjects were recruited between February 2005 and March 2006 by 1) advertisements seeking healthy postmenopausal women to participate in clinical bone research (n = 184) and 2) approaching subjects who had previously been involved in clinical research within our group and had indicated interest in participating in future studies (n = 88). Recruitment for three clinical studies, each with a different BMD eligibility criterion, occurred concurrently. A total of 272 women were assessed for eligibility to participate in the current study. Of these women, 222 did not proceed to randomization, because they did not meet eligibility criteria (n = 85), they decided not to participate (n = 94), or they enrolled in a different study (n = 43). Among the 50 women randomized, one in the zoledronate group withdrew during the study for personal reasons (Fig. 1). The final 2-yr study visit occurred in March 2008.

Protocol

All visits took place at a clinical research facility in a tertiary medical center. Participants were randomly allocated to receive a single administration of either zoledronate 5 mg, given as a 15-min iv infusion in 100 ml 0.9% NaCl, or placebo (100 ml 0.9% NaCl, administered in an identical fashion). No other study medication was administered. Treatment allocations were randomized by the study statistician, using a variable block size schedule, based on computer-generated (Excel 2003) random numbers. To ensure masking, only the statistician had access to treatment allocation. The staff member who prepared the iv infusions had no contact with participants. All the other study personnel and subjects were blinded to treatment allocation throughout. Only the study statistician saw unblinded data, but he had no contact with study participants. The study received ethical approval from the Auckland Ethics

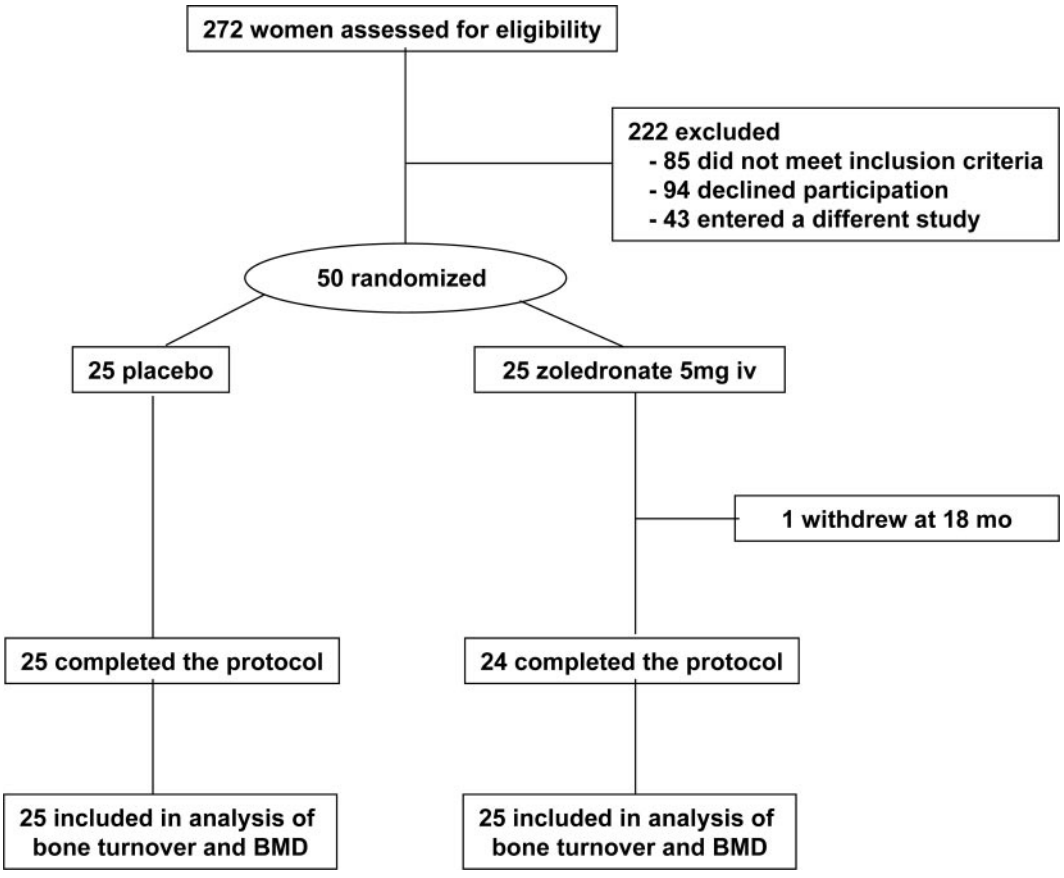

FIG. 1. Flow of subjects through the study.

Committee and was registered with the Australian New Zealand Clinical Trials Registry, ACTRN12605000278639. All participants gave written, informed consent.

The co-primary endpoints were the bone turnover markers serum procollagen type-I N-terminal propeptide (P1NP) and β-C-terminal telopeptide of type I collagen (β-CTX). Secondary endpoints were BMD at lumbar spine, total hip, and total body. The trial protocol specifies a 3-yr follow-up period but includes a prespecified interim data analysis after 2 yr, using the nominal significance level of 0.00082 for either endpoint, calculated as the O'Brien and Fleming spending function (7) using PASS 2002 (NCSS and PASS Number Cruncher Statistical Systems, Kaysville, UT.). All tests were two tailed. With allowance for five subjects to withdraw from each group, a sample size of 50 subjects is adequate to detect differences (with 80% power at the 5% significance level) of at least 89% of 1 SD between the treatment arms.

Bone turnover markers and biochemistry

At baseline and at 3, 12, 18, and 24 months, fasting blood and second-voided morning urine samples were collected and stored at −70 C until they were batch analyzed. Serum osteocalcin, P1NP, and β-CTX were measured using the Roche Elecsys 2010 platform (Roche Diagnostics, Indianapolis, IN), and urine N-telopeptide of type 1 collagen (NTx) by ELISA (Ostex International Inc., Seattle, WA). Coefficients of variation of these markers are as follows: osteocalcin, 5.5%; β-CTX, 5.1%; PINP, 1.9%; NTX, 6.5%. Serum calcium, phosphate, and albumin were measured on a Roche Modular autoanalyzer. Intact PTH was measured using an electrochemiluminescence immunoassay (E170; Roche).

BMD

BMD was measured at baseline and 12, 18, and 24 months at the lumbar spine, left proximal femur, and total body using a Lunar Prodigy dual-energy x-ray absorptiometer (GE Lunar, Madison, WI). BMD measurements were performed by an experienced technician, who is certified by Synarc, the international company that provides bone density oversight for most international osteoporosis drug registration trials.

Statistics

Data were analyzed using procedures of SAS version 9.1 (SAS Institute Inc., Cary NC). Continuous, normally distributed variables were analyzed with a mixed-models ANOVA. Significant main effects of time and treatment and their interaction were created and removed from the final reduced model when they failed to reach statistical significance. In this interim analysis, $P < 0.00082$ was considered statistically significant. Significant main or interaction effects were further explored using the method of Tukey to preserve to overall pairwise error rate. All analyses were performed on absolute changes from baseline values, but BMD and bone turnover marker data are presented as percent change from baseline, for ease of interpretation. To ensure that this analysis met the requirements of statistical significance, a mixed-model analysis of covariance was performed with the baseline level as a covariate. Model reduction and *post hoc* testing proceeded as for the primary analysis of absolute data.

Results

The baseline demographic, bone turnover, and BMD data of the study participants are shown in Table 1. There were no significant differences between the groups for any variable.

Bone turnover markers

The bone turnover data are shown in Fig. 2. Mean values of each marker remained stable throughout the 2 yr in the placebo group. As expected, markers of bone resorption declined substantially within 3 months of zoledronate administration, being 86% [95% confidence interval (CI) = 75–98%] and 59% (45–74%) below those in the placebo group for β-CTX and NTX, respectively ($P < 0.0001$ *vs.* placebo for each marker). After 12 months, the mean value of each of these markers was 64% (95% CI = 43–86%) and 43% (27–60%) below those in the placebo group, respectively ($P < 0.0001$). Similarly, the levels of the markers of bone formation, P1NP and osteocalcin, declined during the first year after zoledronate therapy and were 66% (95% CI = 59–73%) and 49% (40–60%) below placebo levels at 3 months and 37% (16–59%) and 45% (32–58%) below placebo levels at 12 months, respectively ($P < 0.0001$ for all comparisons, zoledronate *vs.* placebo).

TABLE 1. Baseline characteristics of study subjects

	Placebo	Zoledronate
n	25	25
Age (yr)	65 (8)	62 (8)
Weight (kg)	66 (10)	69 (10)
Current smoking, n	1	2
Dietary calcium intake (mg/d)	916 (407)	935 (488)
Serum 25OHD (μg/liter)	34 (12)	29 (7)
P1NP (μg/liter)	58 (21)	55 (16)
Osteocalcin (μg/liter)	24 (9)	23 (5)
β-CTX (μg/liter)	503 (230)	490 (226)
Urine NTx (nmol BCE/mmol Cr)	91 (39)	110 (55)
Lumbar spine BMD (g/cm^2)	1.03 (0.08)	1.06 (0.08)
Total hip BMD (g/cm^2)	0.86 (0.07)	0.85 (0.06)
Total body BMD (g/cm^2)	1.04 (0.06)	1.07 (0.05)

Data are mean (SD), except where indicated. BCE, Bone collagen equivalents; Cr, creatinine; 25OHD, 25-hydroxyvitamin D. To convert 25OHD to nmol/liter, multiply by 2.5.

In the second year of the study, mean levels of each marker of bone turnover in the zoledronate group remained at least 37% below those of the placebo group. Table 2 shows the mean (95% CI) percent differences between the placebo group and the zoledronate group for each marker at each time point during the second year of the study. Between 12 and 24 months, there were highly significant differences between the study groups by treatment allocation ($P < 0.0001$ for each marker, zoledronate *vs.* placebo) but no evidence that the treatment effect changed over time (P for treatment × time interactions > 0.55 for each marker).

BMD

Figure 3 shows the BMD data at lumbar spine, total hip, and total body. After 12 months, BMD in the zoledronate group was higher at each site by 4.8% (3.1–6.5), 3.7% (95% CI = 1.9–5.5%), 2.4% (0.9–4.0%), and 1.2% (0.3–2.0%) at the lumbar spine, total hip, femoral neck, and total body, respectively ($P < 0.0001$ *vs.* placebo at each site). During the second year of the study, there were highly significant differences between the study groups at each skeletal site by treatment allocation ($P < 0.0001$ for each skeletal site, zoledronate *vs.* placebo), but no evidence that the effect differed by time ($0.19 < P < 0.97$ for treatment × time interactions across the skeletal sites, Table 2). None of the between-groups differences at 24 months was lower than the corresponding value at 12 months.

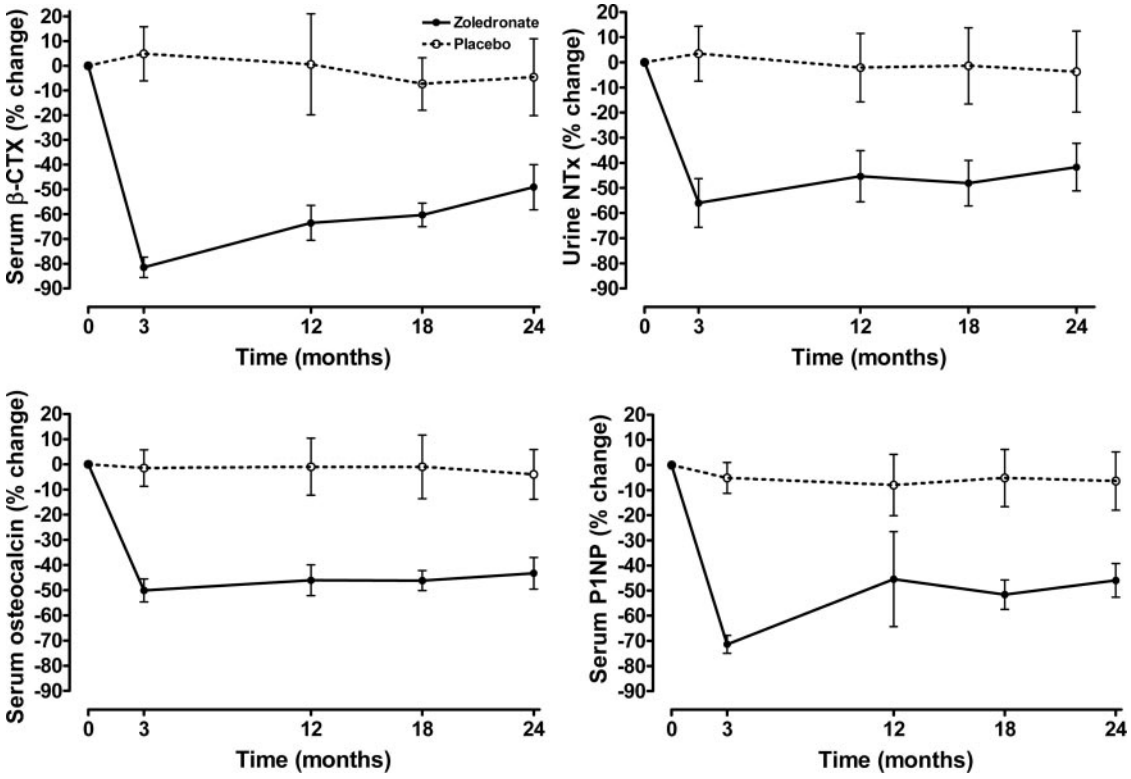

FIG. 2. Effects of a 5-mg dose of zoledronate (*solid lines*) or placebo (*interrupted lines*) on markers of bone turnover over 2 yr in osteopenic postmenopausal women. Data are mean percent of baseline (95% CI).

Biochemistry

Levels of albumin-adjusted serum calcium, serum phosphate, and PTH are shown in Fig. 4. Levels of serum calcium and phosphate declined within the normal range in the group treated with zoledronate and were significantly lower than those in the placebo group during the study; this effect was apparent at 3 months and persisted for the duration of the study (for serum calcium, $P = 0.007$, zoledronate *vs.* placebo; for serum phosphate, $P = 0.006$, zoledronate *vs.* placebo). There was a concomitant rise in PTH in the zoledronate group, although mean levels remained within the normal range throughout the study ($P < 0.0001$, zoledronate *vs.* placebo). These biochemical changes appeared to be diminishing during the final 6 months of the study. There was no effect of zoledronate on serum creatinine ($P = 0.31$, zoledronate *vs.* placebo).

Adverse events

None of the participants developed osteonecrosis of the jaw, incident atrial fibrillation, ocular inflammation, or symptomatic hypocalcemia. No serum calcium values less than 8.32 mg/dl (2.08 mmol/liter) were observed. Five fractures occurred in five participants, three in the zoledronate group (one metacarpal, one forearm, and one fibula), two in the placebo group (one forearm and one toe).

Discussion

Although current recommendations for treatment of osteoporosis with iv zoledronate are for annual administration of a 5-mg dose, the duration of action of this dose has not been rigorously evaluated. The current study demonstrates that the antiresorptive effects of a single 5-mg iv dose of zoledronate persist for at least 2 yr. The changes in markers of bone turnover during the first year of the present study were similar to those reported previously (1, 3), with very substantial decreases (50–80%) in each marker at 3 months and reductions of 40–60% at 12 months. In the second year, levels of each of the markers in the zoledronate group remained significantly lower than those in the placebo group. The magnitude of the between-groups differences were similar at 24 months to those observed at 12 months, although β-CTX levels might be beginning to increase between 18 and 24 months. Similar data were obtained for BMD, which increased as expected in the first 12 months after zoledronate administration (3) and remained higher than that in the placebo group during the second year of the study, such that between-groups differences at each site were similar at 24 months to those at 12 months. These data suggest that dosing intervals for zoledronate of up to 24 months may be associated with antifracture efficacy; this possibility requires evaluation in a clinical trial. In this regard, it is noteworthy that other bisphosphonates, such as risedronate, have been shown to reduce fracture incidence in association with rather smaller effects on both markers and BMD than were observed in the present study (8).

To our knowledge, the current study is the first to rigorously examine the duration of the antiresorptive effects of a single 5-mg dose of zoledronate. We have previously reported that bone turnover markers are stably decreased and increases in BMD maintained, for at least 24 months after the second of two doses of 4 mg iv zoledronate in a placebo-controlled randomized study of

TABLE 2. Between-groups differences in the percent change from baseline in bone turnover markers and BMD between 12 and 24 months

Time (months)	NTx	β–CTX	P1NP	Oc	LS BMD	TH BMD	FN BMD	TB BMD
12	−43 (−60 to −27)	−64 (−86 to −43)	−39 (−53 to −26)	−45 (−58 to −32)	4.8 (3.1–6.5)	3.7 (1.9–5.5)	2.4 (0.9–4.0)	1.2 (0.3–2.0)
18	−47 (−64 to −29)	−53 (−65 to −41)	−47 (−61 to −33)	−45 (−59 to −32)	7.0 (5.3–8.7)	3.8 (2.0–5.6)	2.5 (0.1–5.0)	1.9 (1.0–2.8)
24	−38 (−57 to −19)	−44 (−62 to −26)	−41 (−55 to −27)	−39 (−51 to −28)	5.7 (4.0–7.4)	3.9 (2.2–5.7)	3.9 (3.9–5.9)	1.7 (0.8–2.5)

Data are mean (95% CI) differences between groups in percent change from baseline values. Negative values indicate lower levels in the zoledronate group. FN, Femoral neck; LS, lumbar spine; Oc, osteocalcin; TB, total body; TH, total hip.

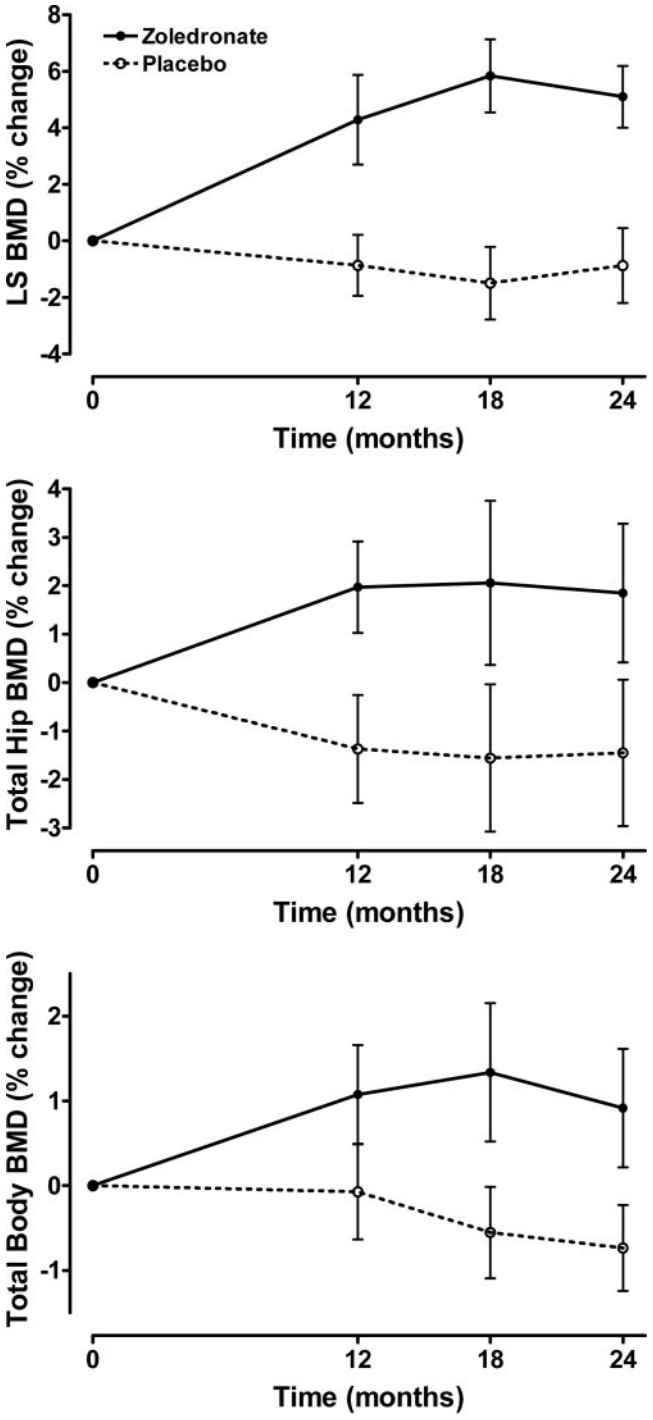

FIG. 3. Effects of a 5-mg dose of zoledronate (*solid lines*) or placebo (*interrupted lines*) on BMDat the lumbar spine (*top*), total hip (*middle*), and total body (*bottom*) over 2 yr in osteopenic postmenopausal women. Data are mean percent change from baseline (95% CI).

osteopenic HIV-infected men (5). Data from uncontrolled observational studies of single doses of zoledronate have produced somewhat conflicting results. In a small study of osteopenic subjects treated with a single dose of 4 mg zoledronate, and daily calcium and vitamin D supplements, serum CTX was decreased by 66% at 12 months but was only 41% below baseline at 18 months, suggesting partial loss of effect, whereas bone-specific alkaline phosphatase, a marker of bone formation, was stably

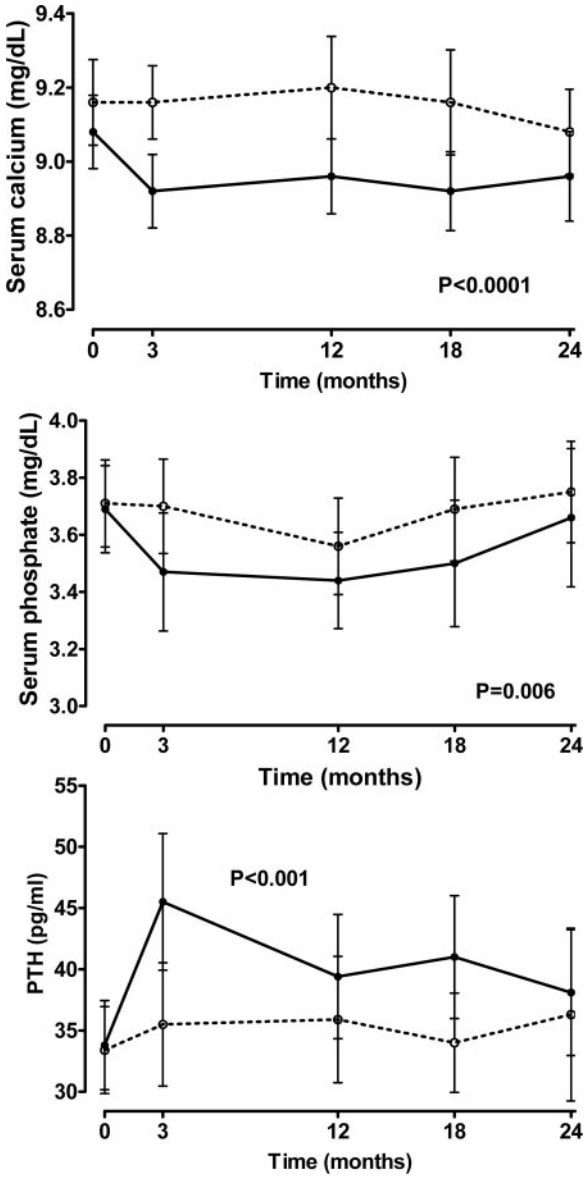

FIG. 4. Effects of a 5-mg dose of zoledronate (*solid lines*) or placebo (*interrupted lines*) on albumin-adjusted serum calcium (*top*), serum phosphate (*middle*), and plasma PTH (*bottom*) over 2 yr in osteopenic postmenopausal women. Data are mean (95% CI). To convert serum calcium to mmol/liter, divide by 4; to convert serum phosphate to mmol/liter, divide by 3.1; to convert PTH to pmol/liter, divide by 9.

decreased between 12 and 18 months (9). In an uncontrolled study of 66 cancer survivors with osteopenia, Brown *et al.* (10) reported that urine NTx was decreased by 40, 32, and 30% at 12, 24, and 36 months, respectively, after a single 4-mg dose of zoledronate. The present, placebo-controlled data demonstrate persistent stable decreases in bone turnover and concomitant stable increases in BMD throughout the skeleton, for up to 2 yr after a single 5-mg dose of zoledronate.

The participants in our study were younger and had higher baseline bone density than those in the phase III zoledronate study, which demonstrated the antifracture efficacy of three annual doses of 5 mg zoledronate in osteoporotic postmenopausal women (1). A detailed analysis of the timing of the onset of fracture protection in that study is not yet available. Although acknowledging that our trial was performed in an osteopenic population and that of Black *et al.* (1) in an osteoporotic population, it is of interest to compare the findings of these studies. In the study of Black *et al.* (1), stable decreases in markers of bone turnover of 30–60% were observed between 12 and 24 months in the zoledronate group, similar in magnitude to those in the present study. BMD changes after 24 months in the study of Black *et al.* (1) were also similar to those we observed at the same time point after a single zoledronate infusion; mean between-group differences in the Black study were 5.9, 4.7, and 3.9% at the lumbar spine, total hip, and femoral neck, respectively, compared with 5.7, 3.9, and 3.9% in the current study.

Our finding that treatment with zoledronate induces mild, sustained secondary hyperparathyroidism may be relevant to a recent report in which histomorphometric analysis of iliac crest bone biopsies from participants in the phase III zoledronate study demonstrated increased bone volume and mineral apposition rate (MAR) in the zoledronate group (11). This finding was not present in studies of other potent bisphosphonates (12–14). MAR reflects the activity of osteoblasts within each remodeling unit and is increased in bone biopsies obtained from animals treated with PTH (15, 16). PTH stimulates osteoblast differentiation and inhibits osteoblast apoptosis (17). It is possible, therefore, that the small but sustained increase in PTH that occurs in response to zoledronate therapy may contribute to the increased MAR observed in the earlier study. A further possibility is that zoledronate may itself prolong osteoblast and osteocyte survival, as has been demonstrated for other bisphosphonates *in vitro* (18).

Optimizing the dosing interval for zoledronate is important. It is clear that medium-term compliance with oral bisphosphonate therapy is poor, although weekly administration is more acceptable to patients than daily ingestion (19). It is likely that even less frequent administration of zoledronate than annually will be more acceptable to patients and hence associated with greater adherence to long-term therapy. Second, decreasing the frequency of administration of zoledronate would substantially decrease the cost of treatment of a single patient and potentially therefore increase access to treatment for a greater number of patients. In a global environment of limited funding for pharmaceuticals, this is an important issue; increasing the dosing interval for zoledronate from 12 to 18 months would reduce the cost of treating an individual patient by 33%. Although the current trial does not provide a definitive rationale for altering the currently approved annual dosing regimen, it has demonstrated that the duration of antiresorptive action of a 5-mg dose of zoledronate considerably exceeds 12 months and provides evidence to support evaluating the antifracture efficacy of dosing intervals of at least 18 months.

Acknowledgments

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This work was supported by funding from the Health Research Council of New Zealand.

A.G., M.B., and I.R.R. designed the study; D.W. and A.H. recruited the participants and collected the data; G.G. supervised the randomization of participants and performed the statistical analyses. All authors participated in writing the manuscript.

Disclosure Summary: A.G., M.J.B., D.W., A.H., and G.G. have nothing to declare; I.R.R has received research funding and speaker and consultancy fees from Novartis, Merck, Procter & Gamble, and Amgen.

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