Phase III Randomized, Placebo-Controlled, Double-Blind Trial of Risedronate for the Prevention of Bone Loss in Premenopausal Women Undergoing Chemotherapy for Primary Breast Cancer

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ABSTRACT

Purpose

Risedronate prevents bone loss in postmenopausal women. The purpose of this study was to determine whether risedronate prevents bone loss in premenopausal women undergoing chemotherapy for breast cancer.

Patients and Methods

Premenopausal women undergoing chemotherapy for breast cancer were treated with oral calcium 600 mg and vitamin D 400 U daily and randomly assigned to receive oral risedronate 35 mg weekly or placebo, with all these therapies beginning within a month of the start of chemotherapy. Most chemotherapy regimens included anthracyclines, taxanes, or cyclophosphamide. Bone mineral density (BMD) was measured at baseline and 1 year. The primary end point was the change in lumbar spine (LS) BMD from baseline to 1 year.

Results

A total of 216 women enrolled; 170 women provided BMD data at 1 year. There was no difference in the mean change or percent change in LS BMD between groups, with a loss of 4.3% in the risedronate arm and 5.4% for placebo at 1 year ($P = .18$). Loss of BMD at the femoral neck and total hip were also similar between treatment groups. Risedronate was well tolerated, with no significant differences in adverse events compared with placebo, except that arthralgias and chest pain were worse in those receiving the placebos.

Conclusion

Risedronate did not prevent bone loss in premenopausal women undergoing adjuvant chemotherapy for breast cancer.

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INTRODUCTION

Women with premenopausal breast cancer are at increased risk for bone loss due to several factors, including cancer therapy-induced bone loss and premature ovarian failure. Chemotherapy has been reported to induce age-related premature ovarian failure in women who are premenopausal at the time of their breast cancer diagnosis, affecting 13% to 77% of women younger than 40 years and 57% to 98% of women older than 40 years.¹ Menopause is accompanied by accelerated bone loss; as a result, these women are at increased risk of fracture at an earlier age.

Several studies have confirmed an increased risk of bone loss in premenopausal women undergoing chemotherapy for breast cancer. Among 27

premenopausal women treated with cyclophosphamide, doxorubicin, and fluorouracil, 41% ceased menses during treatment and had a mean bone mineral density (BMD) 14% lower than women who remained premenopausal, and 7% had a lower BMD than would be expected for a 55-year-old woman.² Another study of premenopausal women undergoing chemotherapy for breast cancer reported a median loss of BMD in the lumbar spine (LS) of 6.3%, with a 3.9% decrease in the femoral neck (FN) and a 3.8% decrease in the trochanter.³ Bone loss was greatest among those women who developed chemotherapy-induced ovarian failure, with a reported 7.7% 1-year loss of BMD at the LS.

In addition to the risk of accelerated bone loss related to chemotherapy, tamoxifen has been reported to decrease BMD in premenopausal women.

Tamoxifen, a selective estrogen receptor modulator known to increase BMD in postmenopausal women, was associated with an annual 1.44% decline in LS BMD in premenopausal women treated with it for 3 years.⁴

Breast cancer itself may also increase skeletal fragility and fracture risk, even in the absence of bone metastases, an effect possibly mediated by the secretion of parathyroid hormone–related protein, chemotherapy, or premature ovarian failure. The annual incidence of vertebral fractures in women after a first diagnosis of breast cancer (without skeletal metastases) was reported at 2.8 times that of the general population, with a 24.5-fold increase in risk for women with recurrent breast cancer and no known skeletal metastases.⁵

Several studies have evaluated the effect of bisphosphonates in women with breast cancer, including clodronate, which is not available in the United States, and zoledronic acid, which is administered by intravenous infusion.^{6,7} However, none of the oral agents currently approved by the United States Food and Drug Administration for osteoporosis prevention have been adequately studied in this high-risk population.

Risedronate is a pyridinyl bisphosphonate approved for the prevention and treatment of postmenopausal osteoporosis.⁸ It has demonstrated efficacy in decreasing the rate of bone turnover and reversing the loss of BMD, with an adverse effect profile that is similar to that of placebo. It was hypothesized that the use of this agent, beginning along with adjuvant chemotherapy, might attenuate the marked bone loss that occurs in women who experience premature ovarian failure as a result of cytotoxic treatment. This controlled trial evaluated the effect of chemotherapy, with or without concomitant risedronate, on BMD in premenopausal women.

PATIENTS AND METHODS

This study was conducted by the North Central Cancer Treatment Group (NCCTG) after approval by the National Cancer Institute (NCI) and the local institutional review boards from participating sites within North America. Informed consent was obtained from all participants before enrollment. The study was funded by the NCI, with supplemental funding from Aventis.

Study Population

Eligible study participants were premenopausal women scheduled to undergo adjuvant or neoadjuvant chemotherapy for primary breast cancer (stages I to IIIB). Premenopausal status was defined as ≤ 6 months since last menstrual period, no prior bilateral oophorectomy, and no treatment with menopausal estrogen therapy. If a total abdominal hysterectomy had been performed, with at least one intact ovary, or if more than 3 months since the last menstrual period had lapsed, then patients must have had documented premenopausal estrogen levels (≤ 1 month before study entry), understanding the limitation of this test. Women must have been at least 18 years of age, with an Eastern Cooperative Oncology Group performance status of 0 (fully active) or 1 (ambulatory and able to carry out light work).⁹

Women were excluded for hypercalcemia, hypocalcemia, an inability to stand or sit upright for at least 30 minutes, known swallowing disorder, BMD T score of ≤ -2.0 at the hip or LS, history of vertebral compression fracture, corticosteroid use at doses more than 5 mg/d of prednisone or equivalent for more than 2 weeks in the prior 6 months, previous treatment with bisphosphonates, diseases affecting bone metabolism (hyperthyroidism, hyperparathyroidism, and hypercortisolism), serum creatinine more than 2.0, malabsorption syndrome, menopausal estrogen therapy, oral contraceptive use, bilateral oophorectomy, pregnancy, active nursing, of childbearing potential unwilling to employ adequate contraception, and having undergone dental extraction, root canal, or dental implants ≤ 3 months before registration.

Women planning dental extraction, root canal, or dental implants during study treatment were also ineligible.

Study Design

In this phase III randomized, placebo-controlled, double-blind trial, participants were assigned to take calcium 600 mg with 400 U of vitamin D per day and were randomly assigned to oral risedronate 35 mg or placebo, weekly for 1 year, beginning within 1 month of the start of chemotherapy. The use of ancillary treatments, as appropriate for symptom control and cancer therapy management, was allowed, except for use of bisphosphonates, estrogen, or selective estrogen receptor modulators other than tamoxifen. Patients were stratified by planned use of tamoxifen, use of taxane therapy, time from last menses (< 3 v > 3 months), and age (< 40 v 40 to 49 v ≥ 50 years).

The primary end point was the change in LS (L2 to L4) BMD observed in patients from baseline to 1 year from study entry. Secondary end points included the average intrapatient change in FN and total hip (TH) BMD from baseline to 1 year, incidence of a reduction in BMD, and frequency and severity of toxicity as measured per the NCI Common Toxicity Criteria. Other secondary end points included the incidence of osteopenia and osteoporosis in the risedronate versus placebo groups at 1 year as defined by the use of standardized T scores calculated from the manufacturer reference standard of each clinical laboratory used in this study. Osteopenia was defined as a standardized BMD score of between 1 and 2.5 standard deviations below the norm at any measured site. Osteoporosis was defined as a standardized BMD score of at least 2.5 standard deviations below the norm at any measured site. Exploratory end points included the comparison of BMD between patients with and without ovarian failure and those with and without tamoxifen use.

Fig 1. CONSORT patient enrollment diagram. BMD, bone mineral density.

The BMD was measured by dual-energy x-ray absorptiometry (DXA) devices at the LS, the FN, and the TH at baseline and 1 year. DXA measurements were obtained at the participating NCCTG locations using local DXA devices so that both of the participant's BMDs were measured at baseline and 1 year from the same machine. DXA precision assessments conducted by the participating NCCTG locations were performed locally.

Adverse events were collected using telephone calls every other month and at the time of participant follow-up visits. These were graded according to the Common Toxicity Criteria at baseline, 6 months, 1 year, and 2 years. Adherence to study medications was assessed by patient questionnaires at 6-month and 1-year follow-up visits.

With an accrual of 200 patients (100 patients per treatment group), a two sample *t* test with a two-sided $\alpha = 0.05$ would have a likelihood of 80% to detect an effect size of one half standard deviation. If data were not normally distributed, Wilcoxon rank sum tests were to be used, slightly decreasing power. No adjustment in power was made for multiple testing, because there is only a single a priori designated test of hypothesis for the primary end point. Secondary end points were based on effect size observed rather than the statistical significance; therefore, adjusting for multiple testing was irrelevant.

Statistical Analysis

The study was expected to accrue 200 assessable patients. However, 170 patients provided BMD data at baseline and 1 year. Analysis of baseline values of the LS BMD indicated a significant difference between arms, hence percent change from baseline was explored for the primary end point. Average values of the percent change from baseline between arms at 1 year were computed and compared using the Wilcoxon rank sum methodology. Linear regression modeling of the BMD at 1 year was used to adjust for covariates of age, age group, treatment arm, planned tamoxifen use, planned taxane use, race, estimated months since last menses, and baseline LS BMD.

The analytic procedures used for the primary end point were applied to the secondary end points of FN and TH BMD. In accordance with the standardized T score, patients were categorized as having incidence of osteopenia and osteoporosis. Further, patients were categorized as having a greater than 5% decrease in BMD from baseline for LS, FN, and TH BMD. The 5% was arbitrary and used as an indication of the extent of BMD loss. Categorized variables were compared using χ^2 methodology. Toxicity data were compared across treatment groups using χ^2 testing and Wilcoxon methodology as appropriate.

Table 1. Patient Characteristics

Characteristic	Risedronate (n = 106)		Placebo (n = 106)		Total (n = 212)		P
	No.	%	No.	%	No.	%	
Age, years							
Mean	43.3		43.6		43.5		.46
SD	5.36		6.09		5.73		
< 40	22	21	25	24	47	22	.77
40-49	73	69	68	64	141	67	
≥ 50	11	10	13	12	24	11	
ECOG performance score							.25
0	93	88	98	93	191	90	
1	13	12	8	8	21	10	
Planned tamoxifen							.72
Yes	62	59	59	56	121	57	
No	24	23	29	27	53	25	
Did not know	20	19	18	17	38	18	
Planned taxane							.83
Yes	64	60	66	62	130	61	
No	35	33	35	33	70	33	
Did not know	7	7	5	5	12	3	
Months since LMP							.45
1 to 3	96	91	99	93	195	92	
> 3-6	10	9	7	7	17	8	
Age at first menses, years							.50
Mean	12.6		12.7		12.6		
SD	1.44		1.45		1.44		
Age at first birth, years							.66
Mean	25.1		25.7		25.4		
SD	6.29		5.66		5.98		
Prior hysterectomy	10	9	5	5	15	7	.18
Prior oral contraceptive	32	30	37	35	69	33	.46
Years of prior OCP use							.90
Mean	8.5		8.4		8.5		
SD	7.33		7.13		7.21		
Chemotherapy groups							
Anthracycline based	45	43	41	39	86	41	.60
Taxane based	4	4	3	3	7	3	
Anthracycline + taxane based	55	52	62	59	117	55	
Other	2	2	0	0	2	1	

Abbreviations: SD, standard deviation; ECOG, Eastern Cooperative Oncology Group; LMP, last menstrual period; OCP, oral contraceptive pills.

Table 2. Study Medication Compliance Throughout the Study

Have You Taken the Proper Amount of Study Medication Each Day?	% of Patients			Wilcoxon <i>P</i>
	Risedronate (n = 98)	Placebo (n = 99)	Total (n = 197)	
Almost always	86.6	88	87.3	.55
Usually	7.8	7.6	7.7	
Occasionally	2.4	1.8	2.1	
Rarely	1.2	0.6	0.9	
Almost never	2.1	2	2.1	

NOTE. The categories listed in this table were derived from patient-completed questionnaires. Eight patients from the risedronate arm and seven patients from the placebo arm did not return the patient compliance questionnaire form. Only patients who returned the questionnaire were used for these calculations.

RESULTS

Between March 2003 and March 2006, 216 patients enrolled onto the study (Fig 1), with 108 patients on each arm. Baseline characteristics were similar for both groups (Table 1). Compliance with the study medication was equivalent in both groups, with 87% of all patients reporting that they “almost always” remembered to take their medication (Table 2).

BMD

The primary end point was the percent change in LS BMD from baseline to 1 year (Table 3). The treatment arm had a higher LS BMD at baseline and at 1 year. However, there was no difference in the percent change from baseline to 1 year between the risedronate and placebo groups. Patients in the risedronate arm lost 4.3% BMD at the LS, compared with a loss of 5.4% for placebo ($P = .18$). Exploratory analysis of the primary end point showed no difference in LS BMD between intended tamoxifen users and nonusers. The percent change from baseline to 1 year was also similar between treatment groups. Among the 122 women who remained amenorrheic at 1 year, there was no significant difference in the mean loss of LS BMD compared with placebo.

Mean values of FN and TH BMD from baseline to 1 year were reported in Table 4. Similar findings were seen at these sites as were seen in the LS, with no statistically significant differences between arms in BMD scores at baseline or 1 year.

Table 5 lists results of the categoric data analysis. The incidence of osteopenia and osteoporosis in the risedronate and placebo groups at 1 year indicate no significant difference in the development of either event, although patients in the risedronate arm were numerically less likely to develop osteopenia or osteoporosis than those in the placebo group. A loss of bone density was arbitrarily defined as a more than 5% inpatient decline from

baseline. There was no significant difference in the occurrence of this loss of bone density at the LS, FN, or TH between groups, although patients in the risedronate arm were numerically less likely to experience a 5% loss of bone density in the LS.

Adverse Events

Severe adverse events were minimal (Table 6). Nine patients on the risedronate arm and five patients from the placebo arm experienced grade 4 adverse events, including anemia, acute respiratory distress syndrome, dyspnea, fever, headache, hypotension, leukopenia, neutropenia, and thrombosis. None of the reported grade 4 or lethal adverse events (toxic shock) seemed to be related to the treatment drug. Arthralgia and chest pain were more common in the placebo group than the risedronate group. Among all other reported symptoms, there was no significant difference between risedronate and placebo. Overall, the most common symptoms, which occurred with similar frequency in both groups, included headache, abdominal pain, flatulence, diarrhea, and constipation.

DISCUSSION

This randomized, placebo-controlled clinical trial provided no substantial evidence that risedronate prevented bone loss, over and above what was observed from a placebo, among premenopausal women with breast cancer undergoing adjuvant chemotherapy. The average decrease in bone density observed in the placebo group of premenopausal women undergoing adjuvant chemotherapy was consistent with that of previously published reports in this population. Placebo-treated patients experienced an average 5.4% loss of bone density from baseline to 1 year at the LS, which falls within the 3.7% to 7.7% range of previously published values at this location.^{3,6} The 2.4% loss of bone density at the FN is also consistent with the 1.5% to 4.6% loss documented in other studies.^{3,6}

The women treated with risedronate experienced a slightly lesser degree of bone loss, raising the question of whether risedronate actually decreases bone loss to a smaller degree than was able to be determined by the patient numbers used in this trial. Risedronate was well-tolerated with similar toxicity profiles between the two treatment groups. Of particular note, since oral bisphosphonates are known to cause dyspepsia, there was not an increased rate of dyspepsia, chest pain, or abdominal pain in the risedronate group.

Most studies that have evaluated the effect of bisphosphonates on BMD in patients with breast cancer have included postmenopausal women.¹⁰⁻¹² Results have consistently demonstrated a preservation of bone density in these women, compared with placebo. Delmas et al¹¹ reported a 2.5% difference in LS BMD at 2 years in 43 women completing 2 years of cyclical treatment with risedronate (equivalent to a daily dose of 5 mg) or placebo. Although risedronate successfully

Table 3. Lumbar Spine (LS) Bone Mineral Density

Measurement Variable	Risedronate	95% CI	Placebo	95% CI	<i>P</i>
LS total at baseline, g/cm ²	1.24	1.20, 1.27	1.19	1.16, 1.22	.03
LS total at 1 year, g/cm ²	1.18	1.15, 1.22	1.12	1.09, 1.15	.008
LS change at 1 year, %	-4.3	-5.46 to -3.22	-5.4	-6.76 to -3.98	.18

Table 4. Total Hip (TH) and Femoral Neck (FN) Bone Mineral Density

Measurement Variable	Risedronate	95% CI	Placebo	95% CI	P
TH					
At baseline, g/cm ²	1.04	1.01 to 1.07	1.02	1.00 to 1.05	.32
At 1 year, g/cm ²	1.02	0.98 to 1.05	1.00	0.97 to 1.03	.41
Change at 1 year, %	-2.7	-3.98 to -1.46	-3.4	-4.43 to -2.28	.40
FN					
At baseline, g/cm ²	0.98	0.94 to 1.03	0.97	0.94 to 1.00	.44
At 1 year, g/cm ²	0.96	0.93 to 1.00	0.94	0.91 to 0.97	.28
Change at 1 year, %	-2.2	-4.11 to -0.33	-2.4	-5.15 to 0.27	.29

prevented bone loss in this study, the study population differs in that eligible participants were newly postmenopausal women (≥ 6 months postmenopausal after chemotherapy and/or radiotherapy).

Three studies have evaluated the effect of bisphosphonates in premenopausal women. Saarto et al⁶ analyzed the effect of oral clodronate on bone loss in 113 premenopausal women scheduled to undergo six cycles of chemotherapy with cyclophosphamide, methotrexate, and fluorouracil. The use of clodronate reduced the amount of bone loss compared with the control group. In this study, women who became amenorrheic lost significantly more bone density at the LS and FN than those who maintained menstruation, in whom change in BMD was marginal (LS $P < .001$; FN $P = .021$). Bone loss occurred at the LS and FN in both groups at 1 year, despite therapy with 1,600 mg/d of clodronate, relatively high doses often reserved for

treatment of osteolytic lesions, hypercalcemia, or bone pain associated with skeletal metastases from breast cancer or multiple myeloma. The different results observed in the clodronate study versus the current study may be related to the more complete ovarian suppression with the combination regimen of cyclophosphamide, methotrexate, and fluorouracil as opposed to the chemotherapy regimens used in this trial.¹³ Another reason for the differences between the results of these two studies may be related to the dose/potency of the two different bisphosphonates used in these two trials.

Powles et al¹⁴ evaluated the effect of a 1,600 mg daily oral dose of clodronate or placebo on 311 patients with newly diagnosed breast cancer starting concurrent chemotherapy or endocrine therapy. Among the 118 premenopausal women included in this analysis, clodronate reduced bone loss at the LS by 2.48% at 1 year, with no

Table 5. Incidence of Osteopenia, Osteoporosis, and Bone Loss at 1 Year

Osteopenia, Osteoporosis, and Bone Loss	Risedronate (n = 106)		Placebo (n = 106)		Total (n = 212)		P
	No.	%	No.	%	No.	%	
Osteopenia							.32
Missing	20		20		40		
Yes (failure)	24	28	30	35	54	31	
No (success)	62	72	56	65	118	69	
Exact 95% CI of success	0.61 to 0.81		0.54 to 0.75				
Osteoporosis							.15
Missing	20		20		40		
Yes (failure)	0	0	2	2	2	1	
No (success)	86	100	84	98	170	99	
Exact 95% CI of success	0.96 to 1.00		0.92 to 1.00				
LS bone loss $\geq 5\%$							.22
Missing	23		29		52		
Yes (failure)	33	40	38	50	71	44	
No (success)	50	60	39	51	89	56	
Exact 95% CI of success	0.49 to 0.71		0.39 to 0.62				
FN bone loss $\geq 5\%$							.40
Missing	41		51		92		
Yes (failure)	20	31	21	38	41	34	
No (success)	45	69	34	62	79	66	
Exact 95% CI of success	0.57 to 0.80		0.48 to 0.75				
TH bone loss $\geq 5\%$							.82
Missing	38		44		82		
Yes (failure)	21	31	18	29	39	30	
No (success)	47	69	44	71	91	70	
Exact 95% CI of success	0.57 to 0.80		0.58 to 0.82				

Abbreviations: LS, lumbar spine; FN, femoral neck; TH, total hip.

Table 6. Adverse Events Reported in More Than 3% of Patients From Baseline to 1 Year

Table 2. Adverse Events Reported in More Than 5% of Patients From Baseline to 1 Year													
Adverse Event	Risedronate (n = 106)						Placebo (n = 106)						P
	Grade 1/2		Grade 3		Grade 4		Grade 1/2		Grade 3		Grade 4		
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	
Arthralgia	0	0	0	0	0	0	1	1	3	3	0	0	.045
Chest pain	0	0	0	0	0	0	2	2	2	2	0	0	.045
Constipation	52	49	1	1	0	0	61	58	0	0	0	0	.19
Headache	40	37	2	2	1	1	48	45	3	3	0	0	.21
Irregular menses	0	0	10	9	0	0	0	0	8	8	0	0	.32
Neutropenia	1	1	2	2	4	4	0	0	1	1	3	3	.37
Leukopenia	0	0	5	5	2	2	0	0	0	0	4	4	.39
Dyspnea	0	0	2	2	0	0	1	1	2	2	1	1	.41
Lymphopenia	0	0	3	3	0	0	0	0	5	5	0	0	.47
Nausea	2	2	3	3	0	0	2	2	1	1	0	0	.47
Infection	2	2	1	1	0	0	1	1	3	3	0	0	.57
Flatulence	46	43	0	0	0	0	31	29	13	12	0	0	.61
Abdominal pain	31	29	2	2	0	0	27	26	3	3	0	0	.62
Anemia	2	2	1	1	1	1	2	2	1	1	0	0	.70
Dyspepsia	5	5	2	2	0	0	6	6	2	2	0	0	.80
Diarrhea	29	28	1	1	0	0	28	27	1	1	0	0	.89
Fatigue	2	2	2	2	0	0	4	4	0	0	0	0	.98

significant effect at 2 years of therapy ($P = .9$), again suggesting that bisphosphonates are less effective in a higher estrogen environment.

In 2007, Gnani et al⁷ published a report on the effect of zoledronic acid for the prevention of cancer treatment–induced bone loss in premenopausal women receiving adjuvant endocrine therapy for breast cancer. A total of 401 premenopausal women with hormone-responsive breast cancer were randomly assigned to ovarian suppression (via a luteinizing hormone–releasing hormone agonist, goserelin) with tamoxifen with or without zoledronic acid or anastrozole with or without zoledronic acid. At 3 years, women without zoledronic acid lost significant bone density at the LS and hip, whereas the BMD of those treated with zoledronic acid remained stable. Although these results are significant, women with ovarian suppression are biologically similar to postmenopausal women; in this setting, the effect of zoledronic acid is more consistent with the effect documented in studies of bisphosphonates in postmenopausal patients with breast cancer.

In the current study, it was determined that 122 patients remained amenorrheic at 1 year. Although this may suggest the occurrence of premature ovarian failure, the time to resumption of menses after chemotherapy is variable, with up to 56% of women experiencing only temporary amenorrhea.¹⁵ Twenty-two percent of the women in this study were younger than 40 years at enrollment and would be more likely to resume menstruation. Ongoing clinical follow-up will be needed to further define whether changes in BMD are correlate with the onset of permanent ovarian failure in this study population.

Although low BMD increases fracture risk, other factors can modify this risk, including the degree of bone mineralization and underlying bony micro-architecture. Clinical factors, such as age, vision, gait, concomitant medications, or other diseases, may also modify the risk of fracture. Studies of risedronate-treated women (without breast cancer) have shown that the fracture risk is similar regardless of whether the increase in BMD is less than 5% or more than 5% from baseline.¹⁶ Therefore, changes in BMD may not be strictly correlated with changes in fracture risk.

Several potential study limitations must be noted. This includes the larger than anticipated drop-out rate. One hundred seventy women providing BMD data at 1 year limited the power of a study anticipated to analyze the results from 200 participants. The study was also designed to assess the effect of risedronate on BMD, not fracture risk. As noted, BMD alone does not completely explain fracture risk, and other clinical factors must be considered on an individual patient basis.

Women with a baseline T score of less than -2.0 were also excluded from the study because they are already at increased risk for fracture. In this situation, therapy for prevention of osteoporosis may be considered clinically appropriate, and treatment with a placebo would not be warranted, possibly placing these patients at undue risk of fracture.

There remains a need for the identification of further potential alternative therapies to prevent bone loss in this patient population. Promising lines of research may involve intravenous forms of therapy with bisphosphonates such as zoledronic acid or other novel agents, such as denosumab¹⁷ or cathepsin K inhibitors.¹⁸

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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