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Zoledronic Acid Effectively Prevents Cancer Treatment–Induced Bone Loss in Premenopausal Women Receiving Adjuvant Endocrine Therapy for Hormone-Responsive Breast Cancer: A Report From the Austrian Breast and Colorectal Cancer Study Group

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ABSTRACT

Purpose
Adjuvant therapy for breast cancer can be associated with decreased bone mineral density (BMD) that may lead to skeletal morbidity. This study examined whether zoledronic acid can prevent bone loss associated with adjuvant endocrine therapy in premenopausal patients.

Patients and Methods
This study is a randomized, open-label, phase III, four-arm trial comparing tamoxifen (20 mg/d orally) and goserelin (3.6 mg every 28 days subcutaneously) ± zoledronic acid (4 mg intravenously every 6 months) versus anastrozole (1 mg/d orally) and goserelin ± zoledronic acid for 3 years in premenopausal women with hormone-responsive breast cancer. In a BMD subprotocol at three trial centers, patients underwent serial BMD measurements at 0, 6, 12, 24, and 36 months.

Results
Four hundred one patients were included in the BMD subprotocol. Endocrine treatment without zoledronic acid led to significant ($P < .001$) overall bone loss after 3 years of treatment (BMD, −14.4% after 36 months; mean T score reduction, −1.4). Overall bone loss was significantly more severe in patients receiving anastrozole/goserelin (BMD, −17.3%; mean T score reduction, −2.6) compared with patients receiving tamoxifen/goserelin (BMD, −11.6%; mean T score reduction, −1.1). In contrast, BMD remained stable in zoledronic acid–treated patients ($P < .0001$ compared with endocrine therapy alone). No interactions with age or other risk factors were noted.

Conclusion
Endocrine therapy caused significant bone loss that increased with treatment duration in premenopausal women with breast cancer. Zoledronic acid 4 mg every 6 months effectively inhibited bone loss. Regular BMD measurements and initiation of concomitant bisphosphonate therapy on evidence of bone loss should be considered for patients undergoing endocrine therapy.

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INTRODUCTION

Adjuvant endocrine therapy in patients with hormone receptor–positive breast cancer is entering a new era in patients with low- and intermediate-risk disease. Tamoxifen has been the standard of care for more than 20 years based on evidence that it reduces the risk of recurrence and improves survival in patients treated for 5 years.[1] However, tamoxifen is also associated with an increased risk of endometrial cancer and vascular adverse events (AEs). Third-generation aromatase inhibitors (AIs) are also being used in the adjuvant setting either as replacement therapy for tamoxifen or as follow-up to tamoxifen therapy in postmenopausal women.[2-6] These compounds can overcome tumor resistance to tamoxifen and have a different safety profile compared with tamoxifen. Although they are generally better tolerated and do not cause endometrial cancer, there is concern about their long-term effects on bone and lipids.[2-5,7]

In contrast to postmenopausal women, ovarian ablation is required to provide complete endocrine suppression in premenopausal women.[8] Although adjuvant chemotherapy with cyclophosphamide, methotrexate, and fluorouracil had

been considered the standard of care in this patient population at the initiation of our trial, adjuvant endocrine therapy with the luteinizing hormone–releasing hormone analog goserelin, either alone or in combination with tamoxifen, had already been shown to be at least as effective as chemotherapy based on cyclophosphamide, methotrexate, and fluorouracil in patients with estrogen-positive tumors with regard to overall and disease-free survival.[9-11] Notably, adjuvant endocrine therapy was associated with a more favorable safety profile and improved quality of life compared with chemotherapy.[12] Thus, recent consensus guidelines developed at the 2003 International Conference on the Adjuvant Therapy of Primary Breast Cancer in St Gallen, Switzerland (as well as its 2005 update) recommend the use of adjuvant endocrine therapy as an alternative to chemotherapy in premenopausal women with hormone-responsive breast cancer.[13] Because successful endocrine suppression is thought to be critical for long-term survival in women with hormonal suppression, there is increasing clinical interest in combining goserelin therapy with an AI to ensure total endocrine suppression in this patient population.

The current study, Austrian Breast and Colorectal Cancer Study Group Trial 12, is the first to investigate the combination of goserelin with an AI in premenopausal women with breast cancer. However, treatment with either goserelin or AIs has been associated with significant loss of bone mineral density (BMD). Premenopausal women administered goserelin for 2 years demonstrated a −5% loss of total body BMD[14]; however, the effects of third-generation AIs, either alone or in combination with goserelin, on BMD in premenopausal women have not been previously investigated.

Although AIs represent a powerful new treatment option for patients with breast cancer, the loss of BMD and the associated risk of skeletal complications must be addressed. Bisphosphonates have been shown to prevent bone loss resulting from chemotherapy-induced ovarian failure in premenopausal women,[15,16] suggesting that the addition of a bisphosphonate to the combination of goserelin plus an AI may prevent bone loss. In particular, intravenous (IV) zoledronic acid has shown promise as a safe and effective therapy for the prevention of cancer treatment–induced bone loss (CTIBL). In preclinical studies, zoledronic acid inhibited bone loss induced by surgical ovariectomy or administration of letrozole in rats.[17] In the clinical setting, zoledronic acid (4 mg IV every 6 months) has been shown to prevent CTIBL in postmenopausal women receiving adjuvant therapy with letrozole,[18] and zoledronic acid every 3 months prevented CTIBL and increased BMD above baseline in men with prostate cancer receiving androgen-deprivation therapy.[19]

This large, phase III trial was designed to assess the benefit of adjuvant treatment with the combination of a goserelin plus either tamoxifen or anastrozole on disease-free and overall survival in premenopausal women with hormone-responsive breast cancer. The first survival results from this trial are expected in 2007. As part of the trial design, a prospectively defined BMD subprotocol was initiated at three centers to quantify the long-term effects of these endocrine treatments on BMD and to prospectively evaluate the effect of concomitant zoledronic acid on BMD in those patients. The results of the BMD subprotocol are presented here.

PATIENTS AND METHODS

Patients

Premenopausal women who had undergone primary surgery for stage I or II estrogen receptor–positive and/or progesterone receptor–positive breast cancer, had less than 10 positive lymph nodes, and were scheduled to receive standard therapy with goserelin for 3 years were eligible for enrollment. Patients were excluded if they had T1a (except yT1a), T4d, or yT4 breast cancer; had a history of other neoplasms or cytotoxic chemotherapy; had received preoperative radiation therapy; had been randomly assigned more than 8 weeks postoperatively; were pregnant and/or lactating; were currently receiving oral contraceptives; had serum creatinine levels ≥ 3 mg/dL; had serum calcium levels less than 8.0 mg/dL or more than 12.0 mg/dL; had received treatment with bisphosphonates or chronic anticonvulsive therapy within 1 year before study entry; had current or prior bone disease; or were receiving chronic corticosteroid therapy. None of the patients received prior adjuvant chemotherapy; however, preoperative chemotherapy was allowed.

Study Design and Treatment Schedule: BMD Subprotocol

Patients were randomly assigned 1:1:1:1 using a 2 × 2 factorial design to receive either goserelin (3.6 mg subcutaneously [SC] every 28 days) plus tamoxifen (20 mg/d orally) ± zoledronic acid (8 mg IV every 6 months) or goserelin (3.6 mg SC every 28 days) plus anastrozole (1 mg/d orally) ± zoledronic acid (8 mg IV every 6 months) for 3 years. Protocol amendments reduced the dose of zoledronic acid to 4 mg and increased the infusion time to 15 minutes after reports of decreased renal function with the 8-mg dose of zoledronic acid.

Patients underwent bone densitometry of lumbar spine (L1 to L4) and trochanter by dual-energy x-ray absorptiometry at baseline and at 6, 12, 36, and 60 months. Data from months 0, 6, 12, and 36 only are presented herein; assessment of the 60-month time point is ongoing. The projectional BMD values are given in grams per centimeter squared, and the individual results are expressed as a T score to place the BMD changes into clinical context. Per the WHO classifications for osteoporosis,[20] osteopenia was defined as BMD between −1 and −2.5 standard deviations below the young adult mean. Osteoporosis was defined as BMD ≥ −2.5 standard deviations below the young adult mean.

Safety was assessed according to the frequency of AEs and changes in laboratory values throughout the study. Changes in renal function were evaluated using serum creatinine values, which were assessed every 3 months.

Statistical Methods

Categoric data are described using frequencies and percentages. Continuous data are described using means ± standard deviations for normally distributed data. Non–normally distributed data are described by median, minimum, and maximum. Differences between treatment groups at baseline were assessed by analysis of variance. Baseline measurements were not handled as explanatory covariates. A linear mixed model with repeated measurements and a random factor was used to determine the effect of zoledronic acid on bone density. All bone density measurements were included in the dependent variable of the model. Thus, it was possible to include all patients in the model even if patients were missing bone density measurements close to random assignment. Furthermore, the mean course of bone density measurements from therapy start to 3 years could be estimated. A first-order autoregressive structure of the variance-covariance matrix was chosen to model dependencies between repeated measurements within patients. Differences among patients were assumed to follow a normal distribution with zero mean, which is equivalent to modeling the patient factor as random. Time from surgery to bone density measurements was included as a continuous covariate in the model, in which linear and quadratic time effects were tested. Bone density measurements were assumed to be equal among all four treatment groups at time of surgery because therapies were initiated after surgery. The assumptions of homogeneity and normally distributed errors were verified by residual plots. The effect of the four treatment groups, linear and quadratic time effects, and the interaction between the treatment groups and the time effects were modeled. The effects of zoledronic acid versus no zoledronic acid, of anastrozole versus tamoxifen, of the interaction between anastrozole/tamoxifen and zoledronic acid, and of subgroup tests were assessed by contrasts.

As an additional sensitivity analysis, differences in BMD measurements and T scores are described by means and evaluated by two-sample *t* tests. The *t* test statistical method is less powerful than the linear mixed model because it

fails to account for potential dependencies in the data because of repeated measures. Nevertheless, it may be more intuitively obvious to physicians.

Calculations were performed using the statistical software SAS (Version 8, 2001; SAS Institute, Cary, NC). All statistical analyses were two sided, and significance was assigned at $P \leq .05$.

RESULTS

Patients

A total of 401 patients were included in the BMD subprotocol. Treatment groups were well balanced with regard to patient demographics and baseline disease characteristics (Table 1). Among all patients randomly assigned, 343 patients were assessable for baseline data (range, −3 to 1.5 months after random assignment), 343 patients were assessable at 6 months (range, 1.5 to 9 months), 326 patients were assessable at 12 months (range, 9 to 21 months), and 114 patients were assessable at 36 months (range, 21 to 39 months). Mean baseline BMD values were not different among treatment groups. At baseline, 75% of patients had normal T scores in the lumbar spine, 23% had osteopenia, and only 1% had osteoporosis. In the trochanter, 79% of patients had a normal T score at baseline, 21% had osteopenia, and less than 1% had osteoporosis. Because of differences in absolute BMD values between patients, different measurement time points, and missing values (Table 1), results are shown as quadratic regression curves, as described in Patients and Methods. Alternative statistical models were applied (data not shown), and all showed similar significant differences between treatment groups.

Change From Baseline BMD

Up to four bone density measurements were made in the trochanter and lumbar spine (L1 to L4), resulting in a total of 1,126 BMD measurements, of which 1,108 to 1,119 measurements were used for modeling BMD and T scores because of missing values. Patients treated with either anastrozole or tamoxifen had significant decreases from baseline BMD over 36 months of treatment (Table 2). The loss of BMD in the lumbar spine and trochanter in patients treated with

Table 1. Patient Demographics and Baseline Disease Characteristics (intent-to-treat population)

Characteristic	Tamoxifen Alone (n = 103)		Tamoxifen + Zoledronic Acid (n = 100)		Anastrozole Alone (n = 94)		Anastrozole + Zoledronic Acid (n = 104)	
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%
Age, years								
Median	46.6		43.8		45.7		44.7	
Range	31.8–54.9		28.1–54.7		25.9–56.2		30.6–55.0	
> 40	85	83	80	80	79	84	80	77
≤ 40	18	17	20	20	15	16	24	23
Cancer stage								
T1a	1	1	0	0	0	0	2	2
T1b	18	17	14	14	19	20	18	17
T1c	56	54	55	55	50	53	58	56
T2	25	24	30	30	23	24	24	23
T3	2	2	0	0	0	0	1	1
Cancer grade								
1	17	17	20	20	11	12	14	13
2	56	54	51	51	54	57	64	62
3	27	26	27	27	25	27	23	22
Unknown	2	2	1	1	2	2	2	2
Lymph node metastases								
Positive	43	42	40	40	35	37	40	38
Negative	59	57	59	59	57	61	62	60
Hormone responsiveness								
ER positive	98	95	98	98	87	93	98	94
PgR positive	91	88	87	87	88	94	94	90
Surgery type								
BC	84	82	78	78	73	78	82	79
MRM	18	17	21	21	19	20	20	19
BMD measurements								
Baseline, n = 343	82		87		79		95	
6 months, n = 331	80		89		75		87	
12 months, n = 318	78		83		73		84	
36 months, n = 114	26		26		25		37	
Median baseline BMD, g/cm^2								
L1-L4	1.058		1.028		1.038		1.002	
Trochanter	0.712		0.707		0.728		0.704	

Abbreviations: ER, estrogen receptor; PgR, progesterone receptor; BC, breast conserving; MRM, modified radical mastectomy; BMD, bone mineral density; L, lumbar vertebra.

Table 2. Overall Change From Baseline in Bone Mineral Density and T Score in the Lumbar Spine and Trochanter From Baseline to 36 Months of Treatment

Treatment	Total No. of Patients	No. of Values at Baseline	No. of Values at 36 Months	Lumbar Spine						Trochanter					
				Estimated* Means			Observed Means			Estimated* Means			Observed Means		
				Baseline	36 Months	*P*	Baseline	36 Months	*P*	Baseline	36 Months	*P*	Baseline	36 Months	*P*
Bone mineral density, g/cm^2															
Tamoxifen alone	103	82	26	1.028	0.954	< .0001	1.058	0.935	< .0001	0.715	0.694	< .0001	0.717	0.681	.1317
Tamoxifen + zoledronic acid	100	87	26	1.028	1.032	.0148	1.018	1.032	.6012	0.715	0.722	.1125	0.720	0.708	.4759
Anastrozole alone	94	79	25	1.028	0.893	< .0001	1.035	0.855	< .0001	0.715	0.664	< .0001	0.732	0.647	.0006
Anastrozole + zoledronic acid	104	95	37	1.028	1.024	.0712	1.011	0.985	.3161	0.715	0.717	.2340	0.700	0.696	.8649
T score															
Tamoxifen alone	103			–0.175	–0.855	< .0001	0.102	–1.020	< .0001	–0.034	–0.151	.0019	–0.023	–0.338	.6721
Tamoxifen + zoledronic acid	100			–0.175	–0.150	.0080	–0.246	–0.147	.7026	–0.034	0.137	.0026	0.046	–0.035	.6721
Anastrozole alone	94			–0.175	–1.365	< .0001	0.849	–1.767	< .0001	–0.034	–0.490	< .0001	0.151	–0.698	.0010
Anastrozole + zoledronic acid	104			–0.175	–0.222	.0562	–0.317	0.565	.2772	–0.034	0.041	.0965	–0.182	–0.153	.9015

*By linear mixed model analysis.

anastrozole was significantly greater than the loss of BMD in patients treated with tamoxifen ($P < .0001$ for lumbar spine BMD and $P < .0001$ for trochanter BMD; Figs 1A and 1B; Table 3). In the absence of zoledronic acid, the overall loss of BMD in the lumbar spine after 3 years of treatment was −14.4% after 36 months ($P < .0001$) for observed data and −9.8% ($P < .0001$) when estimated by the linear model. Overall bone loss was more severe in patients receiving anastrozole/goserelin (observed: −17.4%, $P < .0001$; estimated: −13.1%,

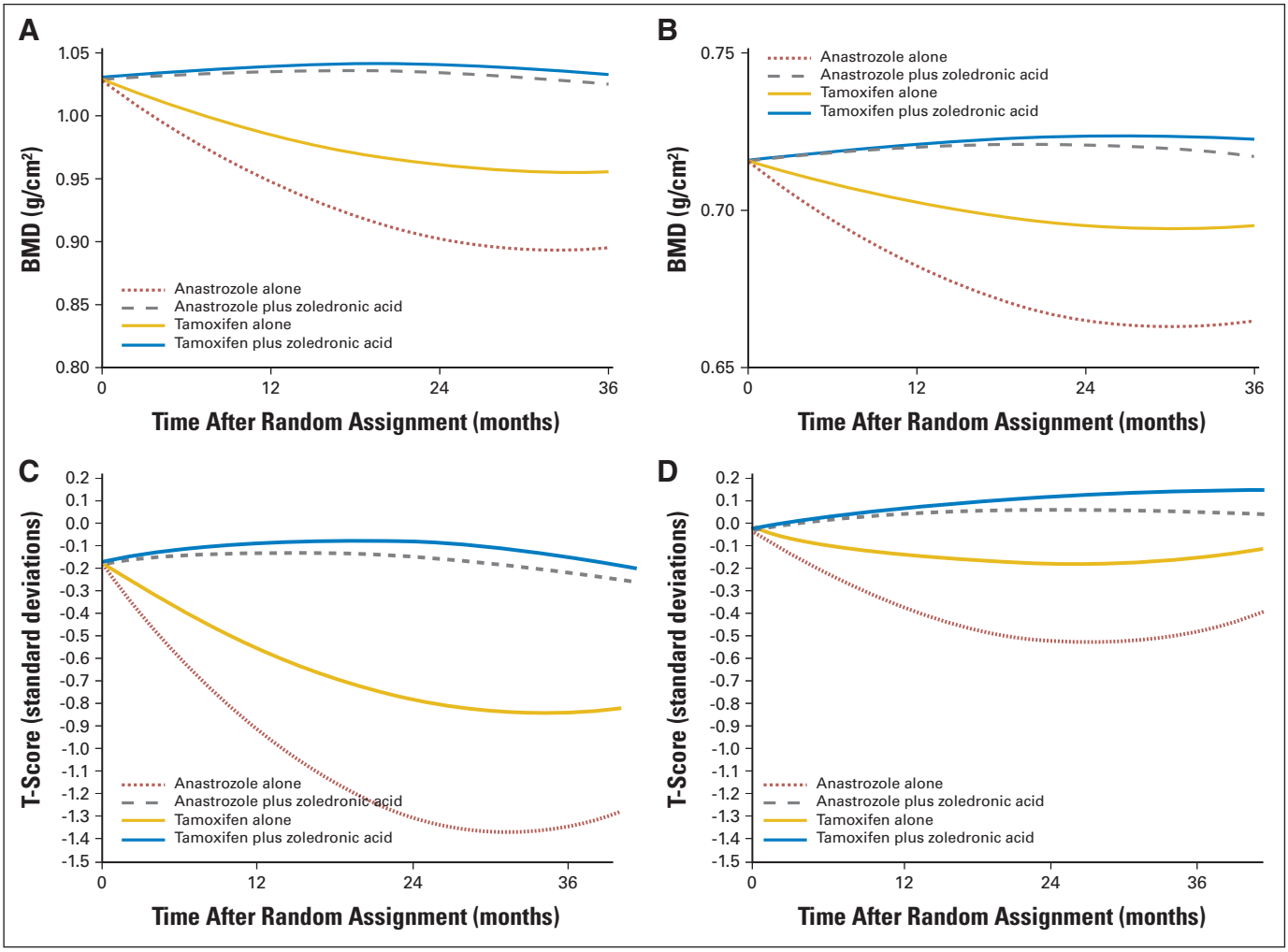

Fig 1. Changes from baseline bone mineral density (BMD) over time in the (A) lumbar spine or (B) trochanter and from baseline T scores over time in the (C) lumbar spine or (D) trochanter of patients treated for 36 months with anastrozole or tamoxifen ± zoledronic acid. Note the change in *y*-axis scale between lumbar spine and trochanter.

Table 3. Parameter Estimates for the Model Presented in Figure 1

Parameter	Tamoxifen Alone		Tamoxifen + Zoledronic Acid		Anastrozole Alone		Anastrozole + Zoledronic Acid	
	Estimate	SE	Estimate	SE	Estimate	SE	Estimate	SE
Lumbar spine change in BMD								
Intercept	1028.3	6.21						
Linear	–4.55	0.38	1.10	0.42	–8.38	0.47	0.69	0.38
Quadratic	0.07	0.01	–0.03	0.01	0.13	0.01	–0.02	0.01
Trochanter change in BMD								
Intercept	715.3	5.42						
Linear	–1.42	0.33	0.57	0.31	–3.52	0.35	0.51	0.30
Quadratic	0.02	0.01	–0.01	0.01	0.06	0.01	–0.01	0.01
Lumbar spine change in T scores								
Intercept	–175.2	56.47						
Linear	–39.51	3.66	10.02	3.22	–76.75	4.03	5.47	3.21
Quadratic	0.57	0.10	–0.26	0.09	1.21	0.10	–0.19	0.09
Trochanter change in T scores								
Intercept	–34.5	58.46						
Linear	–12.53	3.80	7.43	3.70	–37.11	4.06	6.27	3.55
Quadratic	0.25	0.10	–0.07	1.02	0.68	0.11	–0.12	0.10

NOTE. All values are multiplied by 1,000. The estimates of the intercepts are by definition identical for all four therapy groups.
Abbreviation: BMD, bone mineral density.

$P < .0001$) compared with patients receiving tamoxifen/goserelin (observed: −11.6%, $P < .0001$; estimated: −7.2%, $P < .0001$). For trochanter, the overall loss of BMD after 3 years of treatment was −8.2% ($P = .0005$) for observed data and −4.9% ($P < .0001$) when estimated by the linear model. Overall bone loss was more severe in patients receiving anastrozole/goserelin (observed: –11.3%, $P = .0006$; estimated: −7.2%, $P < .0001$) compared with patients receiving tamoxifen/goserelin (observed: −5.1%, $P < .1317$; estimated: −2.9%, $P < .0001$). In contrast, lumbar spine and trochanter BMD remained stable in patients treated with concomitant zoledronic acid (Table 2). Zoledronic acid prevented bone loss in both lumbar spine and hip regardless of endocrine therapy ($P = .4920$ for lumbar spine and $P = .6449$ for trochanter for the comparison of anastrozole plus zoledronic acid *v* tamoxifen plus zoledronic acid; Figs 1A and 1B).

Change From Baseline T Score

Change from baseline T score with 3 years of endocrine therapy was also significant in the absence of zoledronic acid (observed mean difference: −1.4, $P < .0001$; estimated mean difference: −0.9%, $P < .0001$) for lumbar spine. Similar to changes in BMD, overall change in T score was greater for patients treated with anastrozole (observed mean difference: −2.6, $P < .0001$; estimated mean difference: −1.2, $P < .0001$) compared with tamoxifen (observed mean difference: −1.1, $P < .0001$; estimated mean difference: −0.7, $P < .001$; Fig 1C). T scores for the trochanter also decreased from baseline in the absence of zoledronic acid (observed mean difference: −0.6%, $P = .0017$; estimated mean difference: −0.3, $P < .0001$). The magnitude of decrease was greater for anastrozole (observed mean difference: −0.8, $P = .001$; estimated mean difference: −0.5, $P < .0001$) than for tamoxifen (observed mean difference: −0.3, $P = .2335$; estimated mean difference: −0.1, $P = .0019$; Fig 1D).

Treatment-related bone loss was most dramatic in the lumbar spine (Fig 2). After 36 months of treatment with tamoxifen, 46% of patients had osteopenia but no patient had osteoporosis in the lumbar spine, compared with 16% of patients having osteopenia at baseline (Fig 2A). In contrast, among patients treated with anastrozole for 36 months, 54% of patients had osteopenia and 25% had osteoporosis in the lumbar spine, compared with 24% having osteopenia and 1% having osteoporosis at baseline (Fig 2C). Zoledronic acid significantly prevented the decrease in T scores over time. Among patients treated with tamoxifen plus zoledronic acid for 36 months, only 23% had osteopenia and 4% (n = 1) had osteoporosis of the lumbar spine at 36 months, compared with 23% of patients with osteopenia and 1% of patients (n = 1) with osteoporosis at baseline (Fig 2B). Among patients treated with anastrozole plus zoledronic acid, 44% had osteopenia at 36 months (an absolute increase of 15% from baseline), but no patient developed osteoporosis of the lumbar spine (Fig 2D). Similar results were observed in the trochanter (Fig 3), although treatment-related bone loss was less dramatic than in the lumbar spine.

Safety

The combination of zoledronic acid with endocrine therapy was well tolerated. The most common AEs were consistent with the known toxicity profiles of each drug. Specifically, patients treated with tamoxifen reported a greater frequency of hot flashes and vaginal bleeding, whereas patients treated with anastrozole reported a greater frequency of musculoskeletal disorders. Administration of zoledronic acid was associated with the infusion-related flu-like symptoms common to all IV bisphosphonates (namely, nausea, vomiting, fever, and myalgia). These events were mild to moderate in intensity and were primarily limited to the first infusion of the drug. Importantly, there was no evidence of additive toxicity between zoledronic acid and either goserelin/anastrozole or goserelin/tamoxifen.

No fractures or other skeletal-related events were recorded in this trial. Finally, administration of zoledronic acid was not associated with changes in renal function in this patient population. Across a total of 2,904 serum creatinine measurements over 3 years, mean serum creatinine level was 0.78 ± 0.17 mg/dL, and no patient had a serum creatinine value greater than 1.5× the upper limit of normal. No cases of jaw osteonecrosis were reported in this trial.

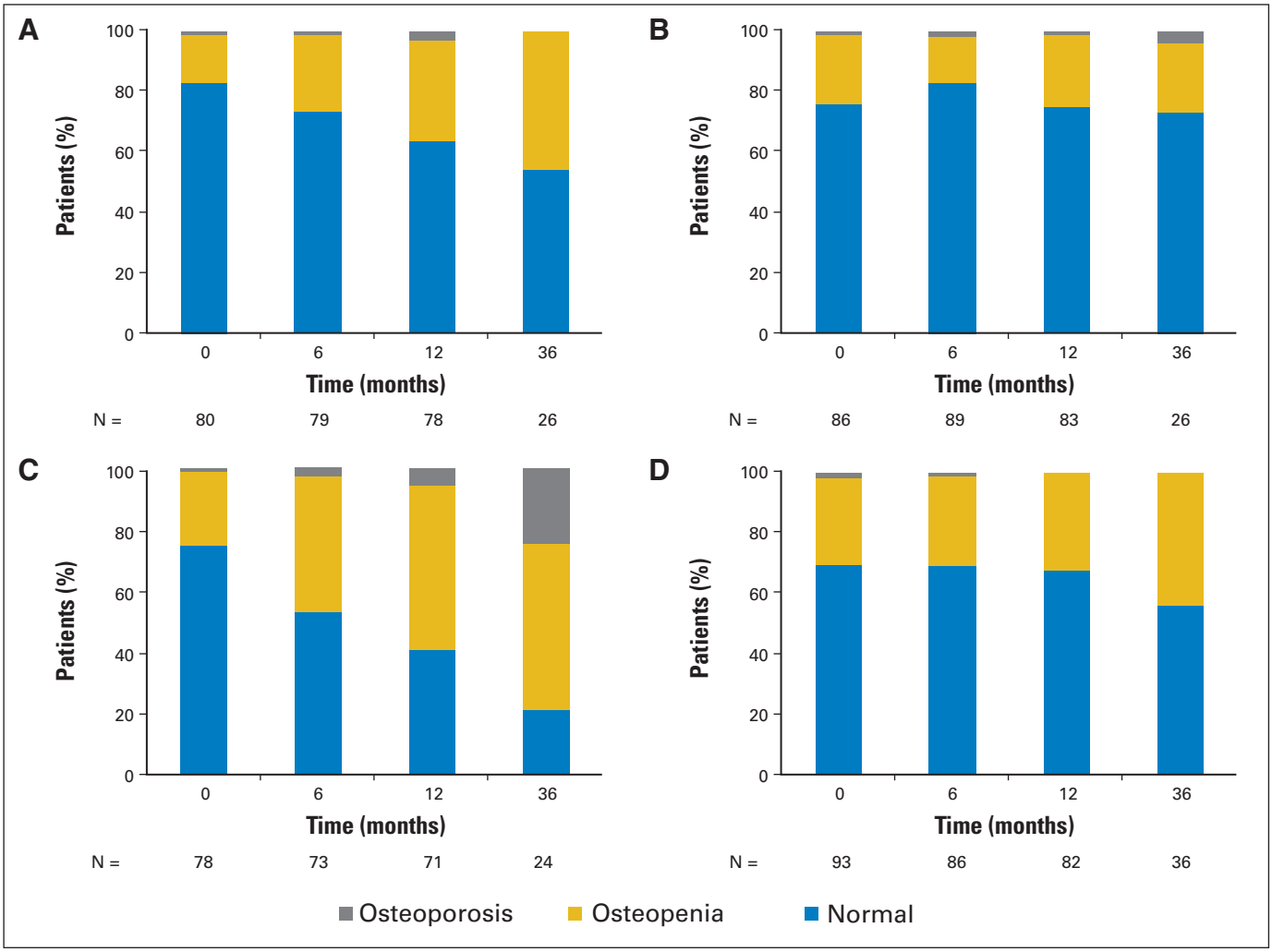

Fig 2. Percentage of patients with normal bone mineral density, osteopenia, or osteoporosis in the lumbar spine of those treated with anastrozole or tamoxifen ± zoledronic acid for 36 months. The change from baseline T score with anastrozole treatment across 36 months is significantly greater than that observed with tamoxifen ($P < .0001$). The addition of zoledronic acid significantly improves T score versus hormone therapy alone ($P < .0001$).

DISCUSSION

CTIBL is a clinically significant problem in patients with breast cancer undergoing adjuvant endocrine therapy. Premenopausal patients treated with tamoxifen 40 mg/d orally plus goserelin 3.6 mg SC every 28 days for 2 years experienced significant loss of BMD.[14] Moreover, long-term treatment with anastrozole has been associated with decreased BMD and increased fracture risk in postmenopausal women.[2,21] In this study of premenopausal women, long-term treatment with goserelin plus either anastrozole or tamoxifen led to statistically significant loss of BMD, and the magnitude of BMD loss was considerably greater with anastrozole compared with tamoxifen. In addition, the proportion of patients with a clinically relevant loss of BMD was significantly higher among anastrozole-treated patients. Loss of BMD was also associated with clinically significant increases in the occurrence of osteopenia and osteoporosis, particularly in the lumbar spine. Furthermore, the severity of CTIBL increased with treatment duration, suggesting that CTIBL will emerge as a significant clinical issue for many women. The American Society of Clinical Oncology Technical Review Panel and the St Gallen Consensus Panel have emphasized the potential utility of anastrozole for treating postmenopausal patients at risk for severe tamoxifen toxicity, but the AEs associated with AIs, including bone loss, remain a concern with long-term treatment.[22] The results of this study indicate that zoledronic acid (4 mg every 6 months) effectively and safely prevents loss of BMD in premenopausal patients treated with either tamoxifen or anastrozole in combination with a luteinizing hormone–releasing hormone agonist. Additionally, zoledronic acid decreased the proportion of patients with particularly severe bone loss in the lumbar spine (ie, those who met the criteria for overt osteoporosis) from 22% to 1% after 3 years of therapy.

This is the first report to demonstrate that the combination of a bisphosphonate with an AI can effectively and safely prevent CTIBL in premenopausal women with early-stage breast cancer. No patient in this study experienced a fracture, which is likely a reflection of the young age of patients. However, among patients treated with anastrozole, the incidence of osteoporosis in the lumbar spine increased to 25% at 3 years, thus putting these patients at substantial risk for vertebral fractures. Decreased BMD is acknowledged to be the single most important predictor of subsequent fractures in postmenopausal

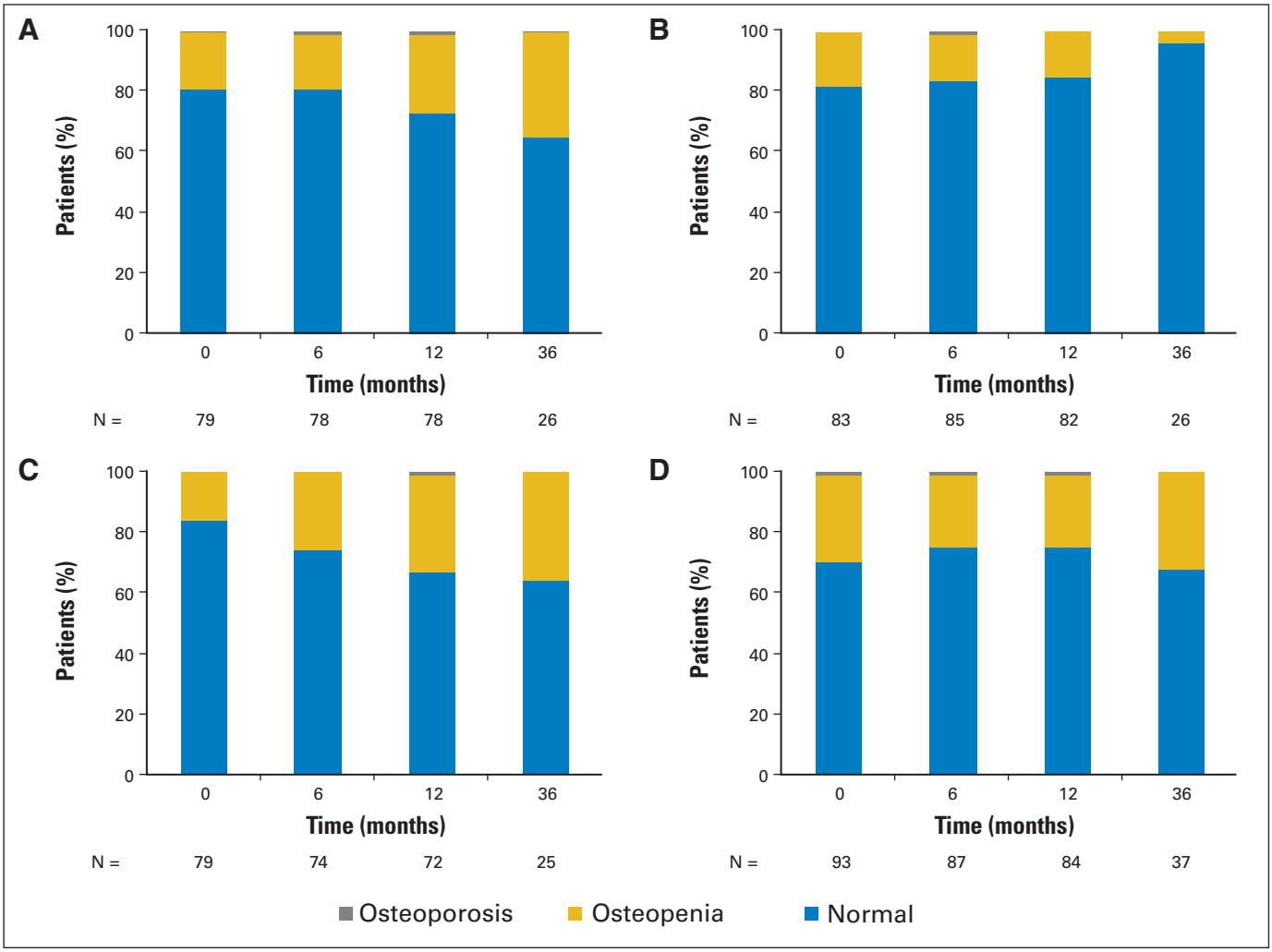

Fig 3. Percentage of patients with normal bone mineral density, osteopenia, or osteoporosis in the trochanter of those treated with anastrozole or tamoxifen ± zoledronic acid for 36 months. The change from baseline T score with anastrozole treatment across 36 months is significantly greater than that observed with tamoxifen ($P < .0001$). The addition of zoledronic acid significantly improves T score versus hormone therapy alone ($P < .0001$).

women with no previous fractures.[23] Furthermore, long-term follow-up studies have shown that patients with vertebral fractures continue to suffer from pain and reduced quality of life 2 to 3 years after the fracture, thus underscoring the long-term clinical consequences of fractures.[24,25]

Recent meta-analyses have suggested that increased BMD as a result of treatment with the oral bisphosphonate risedronate or with raloxifene does not fully explain the decreased risk of fractures observed with antiresorptive therapy, leading some investigators to question whether assessment of BMD is the optimal end point for evaluating bone quality and strength.[26-28] Despite the current level of discussion regarding the correlation between changes in BMD and fracture risk, assessment of BMD remains an accepted and powerful predictive factor for the risk of skeletal complications and represents a validated, noninvasive method for evaluating treatment effect in clinical trials. Regular BMD measurements are recommended for patients undergoing combination endocrine treatment to assess bone health, and initiation of concomitant therapy with a bisphosphonate, such as zoledronic acid, should be strongly considered to prevent skeletal complications in patients who have either a −2.5 T score or who lose ≥ 10% BMD in the first year of treatment. Preliminary results from the Zometa/Femara Adjuvant Synergy Trials, which are evaluating zoledronic acid for the prevention of CTIBL in postmenopausal women with early breast cancer treated with letrozole (2.5 mg daily for 5 years), suggest that up-front, concomitant administration of zoledronic acid is significantly more effective in preserving BMD than delaying initiation of therapy until after evidence of bone loss has occurred.[29]

Many important questions will need to be addressed in future clinical trials, including whether premenopausal patients undergoing adjuvant treatment with AIs may be at greater risk for fractures later in life, what effect treatment cessation may have on subsequent physiologic regulation of bone homeostasis, and whether zoledronic acid also will exert a protective effect against CTIBL induced by cytotoxic chemotherapy. The answers to these questions will provide important information for refining new treatment approaches and improving survival and quality of life in women with breast cancer.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following authors or their immediate family members indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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Appendix

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