Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with early-stage breast cancer: 5-year follow-up of the ABCSG-12 bone-mineral density substudy

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Summary

Background The Austrian Breast and Colorectal Cancer Study Group trial-12 (ABCSG-12) bone substudy assesses zoledronic acid for preventing bone loss associated with adjuvant endocrine therapy and reports on long-term findings of bone-mineral density (BMD) during 3 years of treatment and 2 years after completing adjuvant treatment with or without zoledronic acid. The aim of this substudy is to gain insight into bone health in this setting.

Methods ABCSG-12 is a randomised, open-label, phase III, 4-arm trial comparing tamoxifen (20 mg/day orally) and goserelin (3·6 mg subcutaneously every 28 days) versus anastrozole (1 mg/day orally) and goserelin (3·6 mg subcutaneously every 28 days), both with or without zoledronic acid (4 mg intravenously every 6 months) for 3 years in premenopausal women with endocrine-responsive breast cancer. This prospective bone subprotocol measured BMD at 0, 6, 12, 36, and 60 months. The primary endpoint of the bone substudy (secondary endpoint in the main trial) was change in BMD at 12 months, assessed by dual-energy X-ray absorptiometry in assessable patients. Analyses were intention to treat. Statistical significance was assessed by *t* tests. The ABCSG-12 trial is registered on the ClinicalTrials.gov website, number NCT00295646.

Findings 404 patients were prospectively included in the bone substudy and randomly assigned to endocrine therapy alone (goserelin and anastrozole or goserelin and tamoxifen; n=199) or endocrine therapy concurrent with zoledronic acid (goserelin, anastrozole, and zoledronic acid or goserelin, tamoxifen, and zoledronic acid; n=205). After 3 years of treatment, endocrine therapy alone caused significant loss of BMD at the lumbar spine (–11·3%, mean difference –0·119 g/cm² [95% CI –0·146 to –0·091], p<0·0001) and trochanter (–7·3%, mean difference –0·053 g/cm² [–0·076 to –0·030], p<0·0001). In patients who did not receive zoledronic acid, anastrozole caused greater BMD loss than tamoxifen at 36 months at the lumbar spine (–13·6%, mean difference –0·141 g/cm² [–0·179 to –0·102] *vs* –9·0%, mean difference –0·095 g/cm² [–0·134 to –0·057], p<0·0001 for both). 2 years after the completion of treatment (median follow-up 60 months [range 15·5–96·6]), patients not receiving zoledronic acid still had decreased BMD at both sites compared with baseline (lumbar spine –6·3%, mean difference –0·067 g/cm² [–0·106 to –0·027], p=0·001; trochanter –4·1%, mean difference –0·03 g/cm² [–0·062 to 0·001], p=0·058). Patients who received zoledronic acid had stable BMD at 36 months (lumbar spine +0·4%, mean difference 0·004 g/cm² [–0·024 to 0·032]; trochanter +0·8%, mean difference 0·006 g/cm² [–0·018 to 0·028]) and increased BMD at 60 months at both sites (lumbar spine +4·0%, mean difference 0·039 g/cm² [0·005–0·075], p=0·02; trochanter +3·9%, mean difference 0·028 g/cm² [0·003–0·058], p=0·07) compared with baseline.

Interpretation Goserelin plus tamoxifen or anastrozole for 3 years without concomitant zoledronic acid caused significant bone loss. Although there was partial recovery 2 years after completing treatment, patients receiving endocrine therapy alone did not recover their baseline BMD levels. Concomitant zoledronic acid prevented bone loss during therapy and improved BMD at 5 years.

Funding AstraZeneca (London, UK) and Novartis (Basel, Switzerland).

Introduction

Adjuvant endocrine therapy is now used routinely in patients with hormone-responsive early breast cancer. After surgical excision of the tumour, the aim of adjuvant therapy is to prevent growth of residual tumour cells and extend patient survival. Thus, in postmenopausal patients, the introduction of selective oestrogen-receptor (ER) modulators (eg, tamoxifen) or aromatase inhibitors (eg, letrozole, anastrozole, and exemestane) has substantially improved survival.

In premenopausal women, however, ovarian ablation with surgery or radiation, or reversible ovarian suppression with gonadotropin-releasing hormone (GnRH) analogues is needed to sufficiently inhibit ovarian oestrogen production. In the adjuvant-therapy setting for premenopausal women with advanced hormone-

receptor-positive breast cancer, the combination of a GnRH analogue with tamoxifen improves progression-free survival (PFS) and overall survival compared with ovarian suppression alone.[1,2] In premenopausal women with metastatic breast cancer, the combination of a GnRH analogue and tamoxifen is therefore currently the adjuvant treatment of choice. For premenopausal women with early-stage breast cancer, however, the effects of adjuvant endocrine therapy are still somewhat inconclusive.[3] Additionally, combining a GnRH analogue with tamoxifen in these patients with early-stage breast cancer is at least as effective as cytotoxic chemotherapy and has a more favourable safety profile.[4,5] The 2007 St Gallen expert consensus guidelines recommend ovarian suppression with GnRH analogues in premenopausal women with hormone-responsive early breast cancer.[6] Because aromatase inhibitors have proven better than tamoxifen in postmenopausal women with ER-positive breast cancer, the combination of an aromatase inhibitor with ovarian suppression is being studied in clinical trials as an alternative to tamoxifen in premenopausal patients.

The Austrian Breast and Colorectal Cancer Study Group trial-12 (ABCSG-12) was designed to assess the clinical efficacy of goserelin-induced ovarian suppression plus tamoxifen or anastrozole with or without zoledronic acid in 1803 patients. The first efficacy findings for disease-free survival (DFS), recurrence-free survival (RFS), and overall survival in patients treated with or without zoledronic acid are expected shortly and will be reported separately. A prospective bone-mineral density (BMD) substudy in 404 patients was included in the study design to quantify the long-term effects of endocrine therapy on BMD and to assess the effects of concomitant zoledronic acid on BMD. A 36-month analysis of the BMD substudy showed significant bone loss in patients who received endocrine therapy alone and maintenance of BMD in patients who received endocrine therapy plus zoledronic acid.[7] However, how patients' BMD might change after cessation of adjuvant therapy is not entirely clear. A recent study in premenopausal women with breast cancer who were assigned goserelin or chemotherapy suggests that partial BMD recovery after cessation of goserelin therapy is possible in women who regain ovarian function.[8] Patients who did not recover ovarian function, however, did not have recovery of BMD. The 60-month follow-up data presented here show the BMD status of patients enrolled in the ABCSG-12 bone substudy 2 years after completion of adjuvant therapy.

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Methods

Patients

Patients and methods have been described previously in detail.[7] Briefly, premenopausal women (≥19 years of age) enrolled in the study had received surgery for stage I/II ER-positive or progesterone-receptor (PgR)-positive (or both) breast cancer, had a Karnofsky Index of 70 or greater, fewer than ten positive lymph nodes, and were scheduled to receive goserelin for 3 years. Exclusion criteria included T1a (except yT1a), T4d, or yT4 breast cancer; a history of other tumours or cytotoxic chemotherapy (preoperative chemotherapy was allowed); preoperative radiotherapy; random assignment more than 8 weeks postoperatively; pregnancy or lactation (or both); oral contraception; serum creatinine concentration of 265 µmol/L or more;

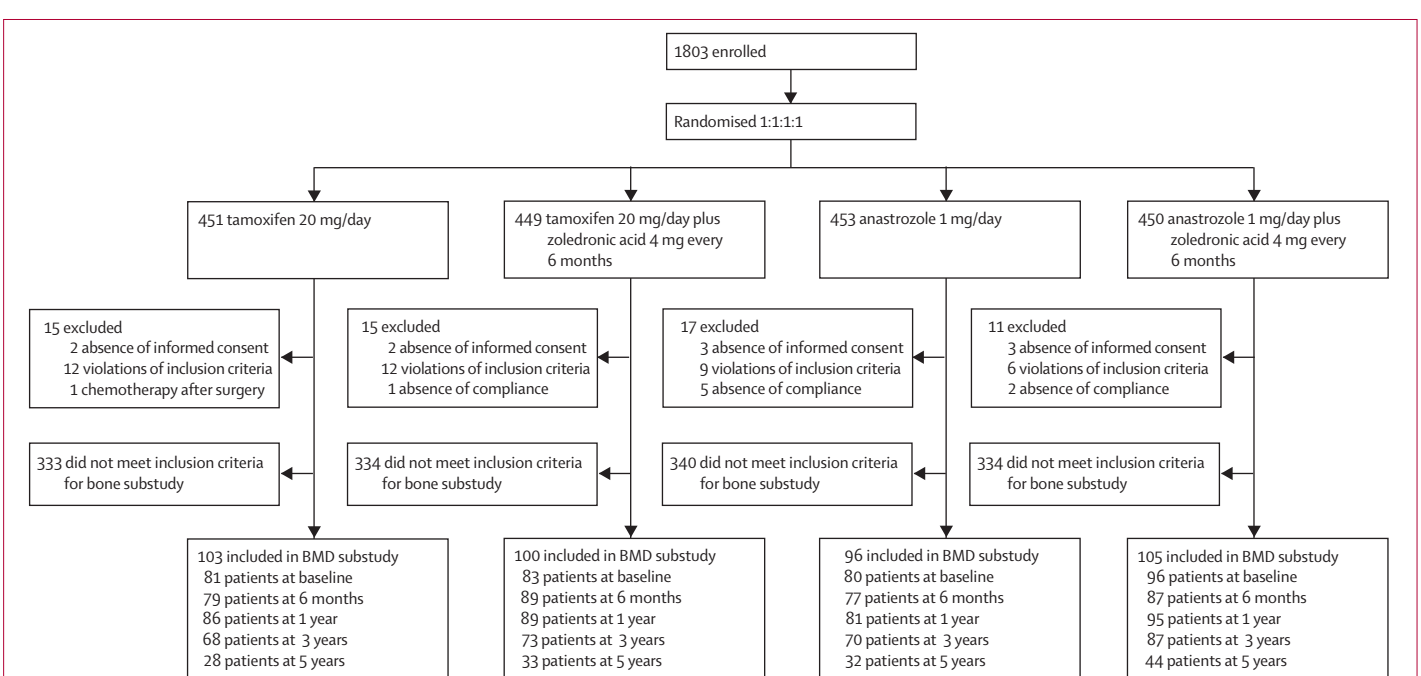

Figure 1: **Trial profile**

	Zoledronic acid (n=205)	No zoledronic acid (n=199)	All patients in BMD substudy (n=404)	Patients not in BMD substudy* (n=390)
Median height (range), cm†	165 (150–180)	165 (145–180)	166 (145–180)	165 (150–187)
Median weight (range), kg‡	63 (45–140)	65 (45–115)	63 (45–140)	65 (36–110)
Median age (range), years	44·5 (28·1–55·0)	46·0 (25·9–56·2)	45·2 (25·9–56·2)	45·6 (28·1–55·43)
≤40 years, n (%)	44 (21)	33 (17)	77 (19)	72 (18)
>40 years, n (%)	161 (79)	166 (83)	327 (81)	318 (82)
Cancer stage, n (%)				
T1	150 (73)	147 (74)	297 (74)	310 (79)
T2	54 (26)	48 (24)	102 (25)	74 (19)
T3	1 (1)	2 (1)	3 (1)	3 (1)
Unknown	0	2 (1)	2 (1)	3 (1)
Lymph nodes involved, n (%)				
0	122 (60)	118 (59)	240 (59)	266 (68)
1–3	67 (33)	73 (37)	140 (35)	107 (27)
4–9	16 (8)	6 (3)	22 (5)	14 (4)
Unknown	0	2 (1)	2 (1)	3 (1)
Cancer grade, n (%)				
1	35 (17)	28 (14)	63 (16)	48 (12)
2	116 (57)	113 (57)	229 (57)	248 (64)
3	51 (25)	52 (26)	103 (25)	91 (23)
Unknown	3 (1)	6 (3)	9 (2)	3 (1)
Oestrogen receptor (ER) expression, n (%)§				
Negative	6 (3)	9 (5)	15 (4)	13 (3)
+	29 (14)	17 (9)	46 (11)	51 (13)
++	81 (40)	86 (43)	167 (41)	144 (37)
+++	89 (43)	85 (43)	174 (43)	179 (46)
Unknown	0	2 (1)	2 (1)	3 (1)
Progesterone receptor (PgR) expression, n (%)§				
Negative	21 (10)	15 (8)	36 (9)	43 (11)
+	21 (10)	34 (17)	55 (14)	72 (18)
++	77 (38)	73 (37)	150 (37)	108 (28)
+++	86 (42)	75 (38)	161 (40)	164 (42)
Unknown	0	2 (1)	2 (1)	3 (1)
ER/PgR^{+++} or ER and PgR^{++}	164 (80)	159 (80)	323 (80)	310 (79)
Per-protocol treatment¶	179 (87)	161 (81)	340 (84)	337 (86)
Surgery, n (%)				
Breast conserving	164 (80)	160 (80)	324 (80)	328 (84)
Mastectomy	41 (20)	37 (19)	78 (19)	59 (15)
Unknown	0	2 (1)	2 (1)	3 (1)

*Patients were from the same trial centres as those providing patients for this substudy, but not enrolled in the BMD substudy. †All patients, n=399; zoledronic-acid group, n=204; no-zoledronic-acid group, n=195. ‡All patients, n=398; zoledronic-acid group, n=203; no-zoledronic-acid group, n=195. §Reiner score for staining: +=10–30%, ++=31–70%, and +++=71–100%. ¶Some control patients were switched to zoledronic acid after 10% bone loss within 12 months or having a fracture, as defined in the protocol amendment.

Table 1: **Patient demographics and baseline disease characteristics**

serum calcium concentration of less than 2 mmol/L or more than 3 mmol/L; bisphosphonate or long-term anticonvulsive therapy within 1 year of study entry; current or previous bone disease; long-term corticosteroid therapy; previous adjuvant chemotherapy; osteomalacia or osteogenesis imperfecta; and any contraindications to one of the trial medications. Patients with pre-existing osteoporosis were excluded. All patients enrolled provided written informed consent. The trial was approved by ethics committees and Institutional Review Boards in all participating institutions. This study was done according to the following good clinical practice guidelines: Good Clinical Practice for Clinical Trials for Medicinal Products in the European Community 1992; Arzneimittelgesetz 1996; Bundesgesetzblatt 185/83; and World Medical Association Declaration of Helskinki 1996.

Patients were randomly assigned to treatment according to the adaptive randomisation method of Pocock and

Simon,[9] by use of a computer program at the Randomisation Centre at the University of Vienna Surgical Department, Vienna, Austria. Patients were stratified by tumour stage and grade, hormone-receptor status (ER, PgR), and lymph-node involvement. Randomised patients were scheduled to receive 3 years of either goserelin (AstraZeneca, Macclesfield, UK; 3·6 mg subcutaneously every 28 days) plus tamoxifen (AstraZeneca; 20 mg/day orally) with or without zoledronic acid (Novartis, Basel, Switzerland; initially 8 mg intravenously), or goserelin (AstraZeneca; 3·6 mg subcutaneously every 28 days) plus anastrozole (AstraZeneca; 1 mg/day orally) with or without zoledronic acid (Novartis; initially 8 mg intravenously). After decreased renal function with the 8-mg dose of zoledronic acid was reported in other studies,[10] the dose of zoledronic acid was changed to 4 mg intravenously every 6 months (consistent with the dose and schedule used in other studies in this setting), and infusion time increased to 15 min. 14 patients in this study received one or two doses of zoledronic acid 8 mg intravenously, and a sensitivity analysis showed that there was no difference in BMD or the number of events compared with the patients who were randomly assigned to the 4-mg dose (data not shown).

Lumbar spine (L1–L4) and trochanter (proximal femur) BMD was assessed by dual-energy X-ray absorptiometry at baseline (3 months before randomisation to 1·5 months after start of treatment) and at 6, 12, 36, and 60 months. Calibrations of dual-energy X-ray absorptiometry machines were standardised between institutions, and quality-assurance processes by routine standardisation continued throughout the study at regular intervals. The BMD reports were blinded and centrally reviewed. T scores were determined according to the WHO definition as standard deviation units from the mean BMD of young healthy women.[11] The BMD classifications, as defined by WHO, were used to operationally define patient groups (normal=T score ≥–1·0; osteopenia=T score between –1·0 and –2·5; osteoporosis=T score ≤–2·5).[11] Renal function was assessed every 3 months by measurement of serum creatinine concentrations, and safety was assessed throughout the study. Patient fracture data were collected via serious-adverse-event reports and case-report forms.

Statistical analysis

The effect of zoledronic acid on BMD was assessed by use of a linear mixed model, including repeated measurements and a random factor, and the dependent variable model included all BMD measurements. Dependencies between repeated measurements within the same patient were modelled by use of a first-order autoregressive structure of the variance-covariance matrix. Time from surgery to

	Zoledronic acid (n=205)				No zoledronic acid (n=199)			
	Mean (SD)	% *vs* baseline	Mean difference from baseline (95% CI)	p*	Mean (SD)	% *vs* baseline	Mean difference from baseline (95% CI)	p*
Lumbar spine								
BMD, g/cm²								
Baseline	1·014 (0·125)	..	..	..	1·048 (0·126)	..	..	..
12 months	1·029 (0·128)	+1·5%	0·015 (–0·011 to 0·041)	0·260	0·971 (0·128)	–7·4%	–0·077 (–0·104 to –0·049)	<0·0001
36 months	1·018 (0·130)	+0·4%	0·004 (–0·024 to 0·032)	0·772	0·929 (0·116)	–11·3%	–0·119 (–0·146 to –0·091)	<0·0001
60 months	1·054 (0·133)	+4·0%	0·039 (0·005 to 0·075)	0·022	0·981 (0·140)	–6·3%	–0·067 (–0·106 to –0·027)	0·001
T score†								
Baseline	–0·294 (1·135)		..	..	0·002 (1·150)		..	..
12 months	–0·167 (1·167)		0·1 (–0·1 to 0·4)	0·295	–0·691 (1·164)		–0·7 (–0·9 to –0·4)	<0·0001
36 months	–0·273 (1·180)		0·0 (–0·2 to 0·3)	0·865	–1·076 (1·055)		–1·1 (–1·3 to –0·8)	<0·0001
60 months	0·051 (1·221)		0·4 (0·0 to 0·7)	0·030	–0·600 (1·278)		–0·6 (–1·0 to –0·2)	0·001
Trochanter (hip)								
BMD, g/cm²								
Baseline	0·710 (0·111)	..	..	..	0·724 (0·106)	..	..	..
12 months	0·716 (0·110)	+0·8%	0·006 (–0·017 to 0·029)	0·616	0·694 (1·069)	–4·1%	–0·030 (–0·053 to –0·007)	0·010
36 months	0·716 (0·103)	+0·8%	0·006 (–0·018 to 0·028)	0·642	0·671 (0·097)	–7·3%	–0·053 (–0·076 to –0·030)	<0·0001
60 months	0·738 (0·114)	+3·9%	0·028 (–0·003 to 0·058)	0·073	0·694 (0·105)	–4·1%	–0·030 (–0·062 to 0·001)	0·058
T score†								
Baseline	–0·077 (1·209)		..	..	0·067 (1·146)		..	..
12 months	–0·006 (1·190)		0·1 (–0·2 to 0·3)	0·576	–0·243 (1·150)		–0·3 (–0·6 to –0·1)	0·015
36 months	0·064 (1·066)		0·1 (–0·1 to 0·4)	0·261	–0·411 (1·009)		–0·5 (–0·7 to –0·2)	0·0002
60 months	0·317 (1·151)		0·4 (0·1 to 0·7)	0·017	–0·138 (1·080)		–0·2 (–0·5 to 0·1)	0·234

BMD=bone-mineral density. *p values were calculated by use of two-sample *t* tests for mean differences from baseline. †T scores are defined as standard deviation units from the mean bone-mineral density of young healthy women.

Table 2: **Overall change from baseline in bone-mineral density and T score at the lumbar spine and hip**

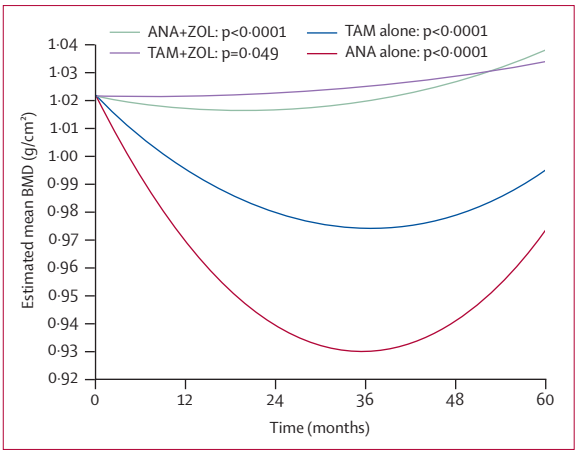

Figure 2: **Changes from baseline to 60 months in bone-mineral density (BMD) of lumbar spine**
Patients were randomly assigned to anastrozole (ANA) or tamoxifen (TAM) with or without zoledronic acid (ZOL; 4 mg every 6 months) for 36 months and then no treatment from 36 to 60 months. Estimated least-square means from the model with quadratic time effects. p values correspond to BMD change from baseline to 60 months (estimated within the model).

bone-density measurements was included as a continuous covariate in the model, in which linear and quadratic time effects were tested. Residual plots were used to verify the model assumptions of homogeneity and normally distributed errors. The effect of the four treatment groups, linear and quadratic time effects, and the interaction between the treatment groups and the time effects were modelled. This model was chosen because it fitted the data best based on Akaike information criterion (AIC),[12] and provided the most information regarding effects on BMD over time, although similar findings were obtained with the other models tested. Contrasts were used to assess the effects of zoledronic acid versus no zoledronic acid, of anastrozole versus tamoxifen, of the interaction between anastrozole and tamoxifen and zoledronic acid, and of subgroup tests. As an additional sensitivity analysis, differences in BMD measurements and T scores were described by means and assessed by two-sample *t* tests. An association between lengthy loss of ovarian function (≥40 months after randomisation) and BMD measurements was modelled by analysis of variance (ANOVA), including zoledronic-acid treatment. The statistical software SAS (version 9.1, 2005; SAS Institute, Cary, NC, USA) was used to do all calculations; all statistical analyses were two-sided, and significance was assigned at p≤0·05.

See Online for webtable 1

The BMD substudy of the main trial was originally designed to detect a difference in BMD at 1 year in BMD-assessable patients relative to baseline between the groups treated with or without zoledronic acid. A cohort of 200 patients (50 in each of the four groups) was considered adequate to detect a 1·5% difference between the two groups with a two-sided *t* test at a 5% significance level, 3·5 common standard deviations, and 85% power. A protocol amendment increased the number of patients to compensate for the potential confounding interaction between age (older versus younger) and zoledronic-acid therapy. Increasing the number of patients to 360 (90 in each of the four groups) was sufficient to detect an interaction defined by a BMD decrease of 0·4% per life-year in the control group and a BMD increase of 0·3% per life-year in the zoledronic-acid group with 80% power, 5% alpha error, 5·5 standard deviations for age, and 13 standard deviations for residuals. Assuming a drop-out proportion of 10%, the protocol amendment increased the number of patients to 400. Analyses were by intention to treat.

The ABCSG-12 trial is registered on the ClinicalTrials.gov website, number NCT00295646.

Role of the funding source

This academic trial received funding in the form of drug support and other funding from both AstraZeneca, Macclesfield, UK (tamoxifen [Nolvadex] and anastrozole [Arimidex]) and Novartis, Basel, Switzerland (zoledronic acid [Zometa]). Neither funding source was involved in the collection, analysis, and interpretation of data, the writing of the report, or the decision to submit for publication. MG, PW, and MM had full access to all of the data in the study and MG had final responsibility for the decision to submit for publication.

Results

Of 1803 patients randomly assigned to the four treatment groups in the ABCSG-12 trial, 404 were prospectively included in the bone substudy (figure 1). Patient demographics and baseline disease characteristics were similar between the treatment groups, and were representative of patients enrolled in the main trial at the same trial centres (table 1). Patients in two of the treatment groups were assigned endocrine therapy (goserelin plus either tamoxifen [n=100] or anastrozole [n=105]) plus zoledronic acid (n=205). Patients in the other two treatment groups were assigned endocrine therapy alone (goserelin plus either tamoxifen [n=103] or anastrozole [n=96]; n=199). 368 of 404 patients (91%) are in follow-up; database lock for this analysis occurred on Dec 3, 2007, with a median follow-up of 60 months (range 15·5–96·6).

A total of 1533 BMD measurements were made at the lumbar spine (L1–L4) and trochanter in 404 patients and all measurements were centrally reviewed. A summary of the number of assessable patients at each BMD assessment is available in webtable 1. Patients who were assigned endocrine therapy plus zoledronic acid had stable BMD at both lumbar spine and trochanter after 36 months (table 2). At 60 months of follow-up, 2 years after ending treatment, patients who were assigned zoledronic acid had increases in mean lumbar-spine and trochanter BMD compared with baseline (+4·0%, mean difference 0·039 g/cm² [95% CI 0·005–0·075], p=0·022 and +3·9%, 0·028 g/cm² [–0·003 to 0·058], p=0·073, respectively). However, in patients who were not assigned zoledronic acid, there was a significant decrease in mean lumbar-spine and trochanter BMD at 36 months (–11·3%, –0·119 g/cm² [–0·146 to

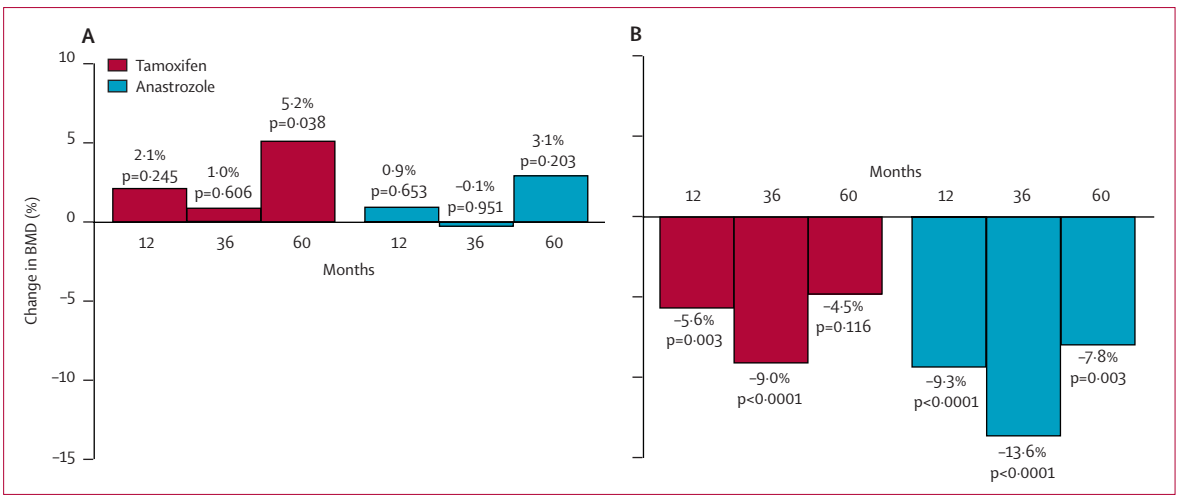

Figure 3: **Percentage change in lumbar spine bone-mineral density (BMD) from baseline to 12, 36, and 60 months**
Patients were randomly assigned to anastrozole or tamoxifen with (A) or without (B) zoledronic acid (4 mg every 6 months) for 36 months and then no treatment from 36 to 60 months. p values were calculated using two-sample *t* tests for mean differences from baseline.

–0·091] and –7·3%, –0·053 g/cm² [–0·076 to –0·030], respectively; p<0·0001 for both). Despite partial recovery of lumbar-spine and trochanter BMD at 60 months, 2 years after cessation of endocrine therapy, BMD remained below baseline levels in these patients (–6·3%, –0·067 g/cm² [–0·106 to –0·027], p=0·001 and –4·1%, –0·030 g/cm² [–0·062 to 0·001], p=0·058, respectively).

By use of a linear regression model that incorporated all available BMD measurements, both BMD and T scores could be accurately predicted throughout the course of follow-up (figure 2). As reported previously, mean lumbar spine BMD was decreased significantly from baseline during 36 months of treatment (figure 2) in patients who were assigned endocrine therapy alone. However, at 60 months (2 years after ending treatment) these patients had partial recovery of BMD, although BMD values remained significantly below baseline levels (p<0·0001 for both anastrozole and tamoxifen). By contrast, patients who were assigned endocrine therapy plus zoledronic acid maintained stable BMD throughout the 36-month treatment period (figure 2), and 2 years after completing therapy had significantly increased lumbar-spine BMD (p=0·030). The zoledronic acid-mediated increase in lumbar-spine BMD was evident in patients assigned tamoxifen plus zoledronic acid and those assigned anastrozole plus zoledronic acid (+5·2%, mean difference 0·053 g/cm² [95% CI 0·000–0·106], p=0·038 and +3·1%, 0·031 g/cm² [–0·018 to 0·079], p=0·203, respectively; figure 3). Similarly, increases were also noted at the trochanter for patients assigned tamoxifen or anastrozole plus zoledronic acid, although the change from baseline was not statistically significant (+5·0%, 0·036 g/cm² [–0·014 to 0·086], p=0·131 and +3·3%, 0·023 g/cm² [–0·017 to 0·062], p=0·255, respectively; data not shown).

The severe BMD losses estimated by the linear model for patients who were assigned endocrine therapy in the absence of zoledronic acid are confirmed by the observed data. Overall, at 36 months, patients who were assigned tamoxifen alone had a 9·0% loss in mean lumbar-spine BMD (mean difference –0·095 g/cm² [95% CI –0·134 to –0·057], p<0·0001) and those assigned anastrozole alone had a 13·6% loss (–0·141 g/cm² [–0·179 to –0·102], p<0·0001; figure 3). Although mean lumbar-spine BMD in these patients had partially recovered at 60 months, it remained below baseline in both groups and signifi-

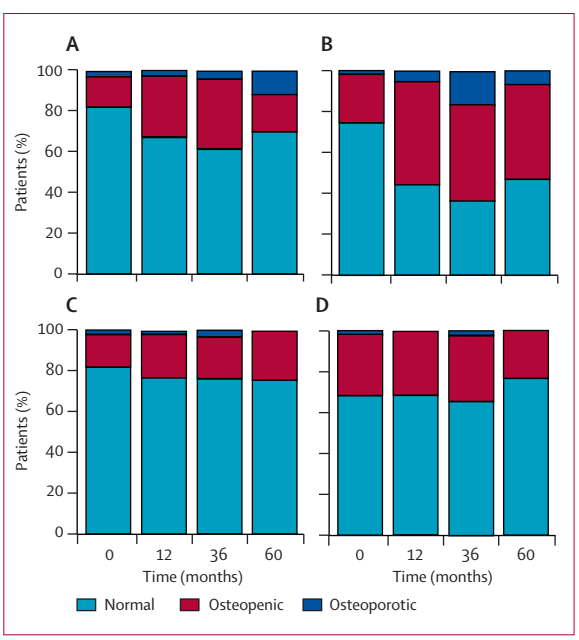

Figure 4: **Percentages of patients with normal, osteopenic, or osteoporotic bone-mineral density T scores at the lumbar spine**
Patients were randomly assigned to (A) tamoxifen alone, (B) anastrozole alone, (C) tamoxifen plus zoledronic acid, or (D) anastrozole plus zoledronic acid. Normal=T score >–1·0; osteopenia=T score –1·0 to –2·5; osteoporosis= T score ≤–2·5.

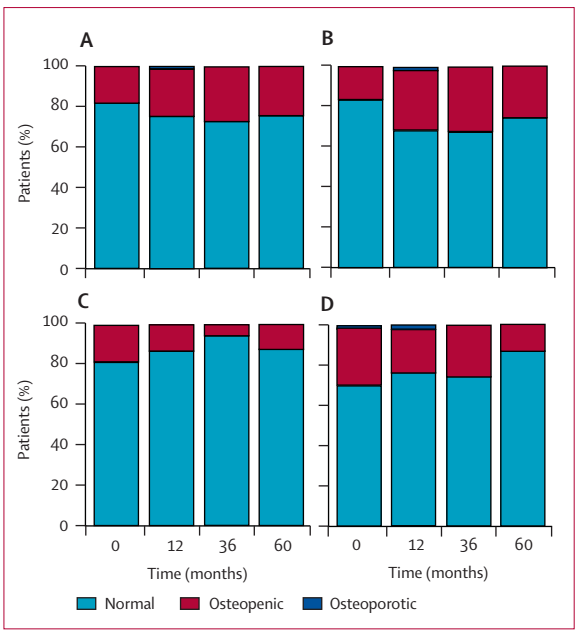

Figure 5: **Percentages of patients with normal, osteopenic, or osteoporotic bone-mineral density T-scores at the trochanter**
Patients were randomly assigned to (A) tamoxifen alone, (B) anastrozole alone, (C) tamoxifen plus zoledronic acid, or (D) anastrozole plus zoledronic acid. Normal=T score >–1·0; osteopenia=T score –1·0 to –2·5; osteoporosis= T score ≤–2·5.

cantly below baseline in the anastrozole-alone group (p=0·003).

In addition to BMD measurements, treatment effects on bone can be monitored by change in a patient's BMD T-score category. The WHO defines BMD T-score categories on the basis of standard deviations from the mean BMD of a healthy, young adult woman.[11] The bone loss associated with endocrine therapy without zoledronic acid was most severe at the lumbar spine (table 2) and resulted in an increase in the proportion of patients with osteopenia and osteoporosis by 36 months (figure 4). In patients who were assigned tamoxifen alone for 36 months, 35% had osteopenia and 3% had osteoporosis. In the same group at 60 months, only 19% were osteopenic, but 11% had become osteoporotic. The increases in osteopenia and osteoporosis were more pronounced in patients who were assigned anastrozole alone: in this group 48% were osteopenic and 17% were osteoporotic at 36 months. Although the proportion of patients with osteoporosis decreased to 6% at 60 months, the proportion of patients with osteopenia remained at 48%.

See Online for webtable 2

Overall, in patients who were assigned the combination of endocrine therapy plus zoledronic acid, the proportion with osteopenia and osteoporosis in the lumbar spine remained constant during 36 months of treatment (osteopenia: 27% at baseline and 28% at 36 months; osteoporosis: 2% at baseline and 2% at 36 months; figure 4). In patients assigned zoledronic acid combined with tamoxifen therapy, the proportion with osteopenia remained relatively constant from 36 to 60 months (21% *vs* 24%), and the proportion with osteoporosis decreased during the same period (3% *vs* 0%). However, in patients who were assigned anastrozole plus zoledronic acid, there was a 10% decrease in the proportion with osteopenia at 60 months compared with the proportion at 36 months (23% *vs* 33%). Importantly, patients in the zoledronic-acid groups who were osteoporotic during therapy at 36 months were no longer osteoporotic at 60 months. The main effects of endocrine therapy with or without zoledronic acid were noted in the lumbar spine and the patterns seen at the trochanter are shown in figure 5. Again, more osteopenia and osteoporosis was seen in the groups without zoledronic acid, but the differences between all four groups are much smaller.

Zoledronic acid combined with goserelin plus tamoxifen or anastrozole was generally well tolerated (table 3). The only significant adverse events associated with zoledronic acid were bone pain (p=0·0003), arthralgia (p=0·013), and fever (p<0·0001). Although this study was done in relatively young patients without pre-existing bone disease and therefore was not powered to assess differences in the proportion of fractures between groups at the 5-year timepoint, two fractures occurred in the groups not assigned zoledronic acid and no fractures were reported for the zoledronic-acid groups. No significant differences in serious adverse events were detected between the groups. Three patients with suspected osteonecrosis of the jaw (ONJ) were reported during the third year of therapy; however, ONJ was ruled out in all three patients after detailed examination of patient dental records by a dentist using the recent ONJ definition from the American Society for Bone and Mineral Research. A complete list of all adverse events is available in webtable 2.[13]

Overall, 101 of 135 patients (75%) in the BMD substudy regained their menses after the end of treatment at 3 years. For the patients for whom long-term follow-up data were available, only 17 of 58 patients (29%) in the no-zoledronic-acid groups and 17 of 77 patients (22%) in the zoledronic-acid groups had longlasting loss of ovarian function after the cessation of therapy. Although there are more precise methods for measuring ovarian function, recovery of menses can provide a fairly accurate estimation of menopausal status. There was no significant association between loss of ovarian function and BMD for lumbar spine and trochanter after adjusting for treatment with zoledronic acid (ANOVA; p=0·70 and p=0·20, respectively).

Discussion

In the BMD substudy of the ABCSG-12, we have shown that zoledronic acid combined with ovarian suppression and with endocrine therapy for premenopausal women with early-stage breast cancer is associated with sustained BMD during 3 years of endocrine therapy and an increase in BMD 2 years after completion of therapy. We also show that much of the bone loss associated with endocrine therapy alone is still present 2 years after completion of

treatment. The findings presented here offer important information related to bone health for premenopausal women undergoing adjuvant endocrine therapy.

Bone loss associated with adjuvant endocrine therapy in premenopausal women with early-stage breast cancer is of substantial clinical concern, because these women typically survive for many years after treatment. Large, population-based studies have shown that any premature decrease in BMD puts women at a distinct disadvantage as they age and increases fracture risk compared with their age-matched peers.[14] In general, a 10% loss in BMD can be equated with 1 standard deviation drop in T score,[15] and can increase fracture risk by 2·6 times.[14] Because fracture risk is affected by peak bone mass and the proportion of bone loss later in life, maintenance of BMD during endocrine therapy is important. Although not all aspects of bone strength can be assessed by BMD measurement alone, this measurement is currently a valid and recognised surrogate for fracture prediction. Other studies have begun to include the measurement of biochemical markers of bone turnover to assess the amount of bone loss; however, a consensus has not been reached regarding which bone marker can best be used to monitor bone loss.

The negative consequences of adjuvant endocrine therapy on bone in premenopausal women have been noted in prospective, randomised studies. For example, 2 years of goserelin therapy in the Zoladex in Premenopausal Patients (ZIPP) trial resulted in significant total-body BMD loss (mean –5·0% [95% CI –0·067 g/cm² to –0·047g/cm²], p<0·001).[16] The effect of adjuvant endocrine therapy on bone is, however, even more pronounced in the present study. Overall, significant bone loss was noted at the lumbar spine after 3 years of ovarian suppression plus tamoxifen or anastrozole (mean for lumbar spine –11·3%, p<0·0001), and bone loss was more severe in patients who were assigned anastrozole compared with those assigned tamoxifen (figure 2).

Currently, very few data are available to suggest how BMD will change after adjuvant endocrine therapy is ended. Some evidence can be obtained from the ZIPP study. Patients receiving goserelin alone had a modest BMD recovery 1 year after treatment cessation, yet those receiving goserelin plus tamoxifen or tamoxifen alone continued to lose BMD.[16] In the current study, patients receiving endocrine therapy alone (ie, goserelin plus tamoxifen or anastrozole) had partial BMD recovery 2 years after completing therapy, but their BMD remained significantly lower than baseline BMD (mean for lumbar spine –6·3%, p=0·001). Indeed, the proportion of patients who developed osteoporosis at the lumbar spine in both the tamoxifen and anastrozole groups at 36 months remained substantial 2 years after ending therapy. A more unexpected finding was that the proportion of patients with osteoporosis actually increased in the tamoxifen-alone group. Although tamoxifen is often thought to be bone protective in postmenopausal women, because of its effect as a partial oestrogen agonist on bone, BMD levels typically decrease in these patients when tamoxifen is discontinued.[17] In the ABCSG-12 trial, goserelin effectively suppressed ovarian function during therapy, but 75% of patients regained ovarian function after cessation of therapy. Consistent with the known effects of tamoxifen withdrawal in the postmenopausal setting, the post-treatment increase in osteoporosis in the tamoxifen-alone group might have been due to the patients who did not regain ovarian function, which would be consistent with early induction of menopause.

At 5 years of follow-up, it is not possible to assess whether these women will ultimately regain their baseline BMD, or whether any BMD improvement will be sufficient to prevent fractures in the future. Because bone strength, and therefore fracture resistance, is determined by both BMD and bone structural properties,[18,19] the unknown long-term effects of endocrine therapy on bone

	Zoledronic acid (n=205)	No zoledronic acid (n=199)	p†
Adverse event, n (%)*			
Bone pain	73 (36)	39 (20)	0·0003
Arthralgia	58 (28)	35 (18)	0·013
Depression, sleeping disorders	43 (21)	37 (19)	0·618
Tiredness	29 (14)	25 (13)	0·663
Headache	26 (13)	21 (11)	0·538
Cutaneous reaction	17 (8)	15 (8)	0·855
Fever	23 (11)	1 (1)	<0·0001
Nausea	14 (7)	9 (5)	0·392
Hypertonia	12 (6)	8 (4)	0·493
Eye problems	7 (3)	9 (5)	0·618
Osteonecrosis of the jaw‡	0	0	..
Fractures	0	2 (1)	0·493
Renal failure	0	0	..
Serious adverse event, n (%)§			
Endometrial hyperplasia/polyps	16 (8)	19 (10)	0·598
Vaginal bleeding/discharge	8 (4)	3 (2)	0·221
Cutaneous reaction	5 (2)	3 (2)	0·724
Secondary cancers	3 (2)	3 (2)	1·000
Liver/gall bladder	1 (<1)	4 (2)	0·210
Pulmonary infection	1 (<1)	3 (2)	0·366
Tendonitis	0	2 (1)	0·242
Ligament rupture/meniscus rupture	0	2 (1)	0·242
Fractures	0	2 (1)	0·242
Depression, sleeping disorder	0	1 (1)	0·499
Peripheral neuropathy, fibroma	0	2 (1)	0·493
Venous thrombosis	1 (<1)	0	1·000

*Adverse events include events judged to be potentially related to treatment. †p values are for the comparison of zoledronic acid *vs* no zoledronic acid (Fisher's exact test). ‡Three patients were initially suspected of having osteonecrosis of the jaw; however, a detailed examination of dental records ruled this out. §Serious adverse events include all events in ≥4 patients or those judged to be potentially related to treatment.

Table 3: **Selected adverse events and serious adverse events on treatment**

microarchitecture might be of great importance. In large, population-based studies, both osteopenia and osteoporosis have been associated with increased fracture risk in postmenopausal women.[20] It is now well understood that in postmenopausal women a previous fracture increases the risk of subsequent fractures, and preventing bone loss and fractures during therapy will probably also decrease the risk of future fractures. Additionally, other clinical risk factors can increase fracture risk, including previous fracture, age greater than 65 years, family history of hip fracture, low body-mass index, corticosteroid use for more than 6 months, and smoking.[21] Further compounding the fracture risk in women with breast cancer, aromatase-inhibitor therapy has been shown to profoundly decrease BMD and significantly increase fracture incidence in postmenopausal patients.[22–24] Taken together, this might suggest that the substantial decrease in oestrogen concentration and rapid BMD loss noted in premenopausal patients receiving endocrine therapy might also ultimately result in increased fracture incidence as this population ages. In the current study, only two fractures were reported in patients who did not receive zoledronic acid and no fractures were reported in the zoledronic-acid groups. Although the fracture incidence in patients who were assigned endocrine therapy alone is relatively low thus far, it will be interesting to monitor the long-term proportion of fractures in these two groups to establish whether substantial fracture prevention is associated with zoledronic-acid therapy. Such findings might have important consequences for overall fracture risk as these women enter menopause and begin to lose bone from natural oestrogen deficiency. Furthermore, many of these patients will probably begin menopause prematurely, which can also negatively affect fracture risk.

In the 60-month follow-up, patients who were assigned ovarian suppression with endocrine therapy plus zoledronic acid maintained stable BMD during 36 months of treatment and had increased BMD during the 2 years after therapy completion. During this time, patients who were osteoporotic at baseline and were assigned zoledronic acid became osteopenic, and more patients who were assigned zoledronic acid had normal BMD after 5 years than those not assigned zoledronic acid. Additional evidence for the efficacy of zoledronic acid for preventing bone loss during endocrine therapy comes from studies in postmenopausal women with breast cancer receiving adjuvant aromatase-inhibitor therapy. In the three companion Zometa-Femara Adjuvant Synergy Trials (Z-FAST, ZO-FAST, E-ZO-FAST), patients received aromatase-inhibitor therapy combined with either immediate zoledronic acid treatment or delayed zoledronic acid (ie, after a fracture or after BMD T score decreased to –2·0).[25–27] Patients who received immediate zoledronic acid treatment had significant and progressive increases in BMD, and had fewer fractures overall than patients who did not receive zoledronic acid ($p<0·0001$ for all). Furthermore, data on disease recurrence suggest that early treatment with zoledronic acid might extend the time to local and distant disease recurrence.[28]

In addition to preventing bone loss, there is a substantial amount of preclinical and early clinical evidence showing that zoledronic acid has antitumour properties. These promising findings have led to several ongoing studies that will ascertain the benefit of combining zoledronic acid with chemotherapy regimens. In fact, the main study of the ABCSG-12 trial (n=1803) was designed to identify the effects of ovarian suppression plus endocrine therapy with or without zoledronic acid on DFS, RFS, and overall survival, with bone metastasis-free survival as an exploratory endpoint in premenopausal women with breast cancer. Findings from the ABCSG-12 trial, presented at the 2008 annual meeting of the American Society of Clinical Oncology (ASCO; Chicago, IL, USA), showed that zoledronic acid combined with endocrine therapy significantly improved DFS and RFS beyond that achieved with endocrine therapy alone ($p<0·015$ for both).[29] Furthermore, two clinical trials in Germany, Postoperative Use of Zoledronic Acid in Breast Cancer Patients After Neoadjuvant Chemotherapy (NATAN) and Simultaneous Study of Gemcitabine-Docetaxel Combination Adjuvant Treatment, as well as Extended Bisphosphonate and Surveillance-Trial (SUCCESS), are investigating whether zoledronic acid in combination with standard cytotoxic chemotherapy will improve DFS in patients with breast cancer. An international study in women with stage II/III breast cancer, Does Adjuvant Zoledronic Acid Reduce Recurrence in Breast Cancer (AZURE), will establish whether zoledronic acid combined with standard chemotherapy will improve DFS and bone metastasis-free survival compared with standard chemotherapy alone.[30]

Contributors

MG, HS, and RJ developed the protocol. MG, FK, PD, HS, RG, and PW took part in writing the report and PD took part in proofreading. MG and HS contributed to literature searches. MG and GS took part in interpretation of data. CMe, MS, HK, FP, GL-E, BM, GS, EK, FF, JCP-S, and VB-R took part in data collection. PW and MM did the statistical analysis. MG, PD, and PW contributed to the generation of tables and figures. MG and RJ coordinated the trial. All authors reviewed and approved the report.

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Conflicts of interest

MG has received research support from, and served as a consultant for, AstraZeneca (goserelin [Zoladex], tamoxifen [Nolvadex], anastrozole [Arimidex]), Novartis (zoledronic acid [Zometa]), Roche, Sanofi-Aventis, and Amgen, and has received lecture fees and honoraria for participation in advisory boards from AstraZeneca, Novartis, Sanofi-Aventis, Roche, and Pfizer. GS has received lecture honoraria from AstraZeneca and Novartis. All other authors declared no conflicts of interest.

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