Skeletal effects of exemestane on bone-mineral density, bone biomarkers, and fracture incidence in postmenopausal women with early breast cancer participating in the Intergroup Exemestane Study (IES): a randomised controlled study

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Summary

Background **Tamoxifen preserves bone in postmenopausal women, but non-steroidal aromatase inhibitors accelerate bone loss and increase fracture risk. We aimed to study the effect on bone health in a subgroup of women included in the Intergroup Exemestane Study (IES), a large randomised trial that compared the switch to the steroidal aromatase inhibitor exemestane with continuation of tamoxifen in the adjuvant treatment of postmenopausal breast cancer.**

Methods **Results were analysed from 206 evaluable patients from the IES, in which postmenopausal women with histologically confirmed and completely resected unilateral breast cancer (that was oestrogen-receptor positive or of unknown status), who were disease-free after 2–3 years of treatment with tamoxifen were randomised to continue oral tamoxifen 20 mg/day or switch to oral exemestane 25 mg/day to complete a total of 5 years of adjuvant endocrine therapy. The primary endpoint was change in bone-mineral density (BMD) assessed by dual energy X-ray absorptiometry. Changes in biochemical markers of bone turnover were also analysed in this substudy, and the incidence of fractures in the entire study reported. The IES is registered on the Current Controlled Trials website http://www.controlled-trials.com/ISRCTN11883920.**

Findings **Within 6 months of switching to exemestane, BMD was lowered by 0·051 g/cm³ (2·7%; 95% CI 2·0–3·4; p<0·0001) at the lumbar spine and 0·025 g/cm³ (1·4%; 0·8–1·9; p<0·0001) at the hip compared with baseline. BMD decreases were only 1·0% (0·4–1·7; p=0·002) and 0·8% (0·3–1·4; p=0·003) in year 2 at the lumbar spine and hip, respectively. No patient with BMD in the normal range at trial entry developed osteoporosis. Bone resorption and formation markers increased at all time points in women receiving exemestane (p<0·001). With a median follow-up in all IES participants (n=4274) of 58 months, 162 (7%) and 115 (5%) patients in the exemestane and tamoxifen groups, respectively, had fractures (odds ratio 1·45 [1·13–1·87]; p=0·003).**

Interpretation **These results indicate that the increase in survival shown previously with the IES switch strategy is achieved at the expense of some detriment to skeletal health, so the risk-benefit ratio to women needs to be individually assessed.**

Lancet Oncol 2007; 8: 119–27

Published Online January 26, 2007 DOI:10.1016/S1470-2045(07)70003-7

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Introduction

The routine use of tamoxifen for the adjuvant treatment of oestrogen-receptor-positive early breast cancer has been challenged by experts after the development of highly specific inhibitors of aromatase. This enzyme enables the conversion of androgens to oestrogens in peripheral tissues, the adrenal glands, and breast tumours. These agents include the reversible non-steroidal inhibitors anastrozole and letrozole, and the steroidal inactivator exemestane. Large randomised trials have shown that all three agents are more effective than tamoxifen alone at preventing breast cancer recurrence, and have fewer thromboembolic complications or gynaecological side-effects, including the development of endometrial cancer.[1–4]

However, owing to the previously described link between residual oestrogen concentrations and fracture risk in postmenopausal women,[5] profound suppression of biologically available oestrogens associated with the use of aromatase inhibitors was expected to increase the rate of bone loss and consequent fracture risk. Further bone-mineral loss leading to osteoporosis and subsequent fractures is an important health problem in postmenopausal women. By contrast, tamoxifen is known to have oestrogen agonist effects on bone and typically prevents postmenopausal bone loss,[6,7] and might reduce the risk of osteoporotic fractures.[8]

Reports have confirmed that non-steroidal aromatase inhibitors increase the rate of bone turnover, accelerate loss of bone as measured by bone-mineral density (BMD), and increase the incidence of fractures.[1,9,10] Although exemestane also has similar inhibitory effects to these drugs on the aromatisation of androgens to oestrogens, a weak but potentially important anabolic effect of exemestane metabolites—which might lead to decreased bone resorption—has been shown in animal studies.[11]

The role of exemestane in the adjuvant treatment of postmenopausal breast cancer has been investigated in the Intergroup Exemestane Study (IES). In this study, women continuing in remission after 2–3 years of

adjuvant tamoxifen were randomised to continue tamoxifen to 5 years (standard practice), or switch to exemestane until the completion of 5 years of adjuvant treatment.[3] Clear benefits in terms of both disease-free survival and distant recurrence-free survival were shown, and have been confirmed in subsequent updated analyses.[12,13] Therefore, the therapeutic strategy of switching from tamoxifen to exemestane after 2–3 years has become an approved and widely used method of treating early postmenopausal breast cancer. In the IES, quantification of the previously unknown effects of the switch strategy on bone health was deemed a priority. In a detailed bone subprotocol, changes in BMD and bone metabolism were measured to assess this potentially important adverse effect of aromatase-inhibitor use. The 24-month results of this substudy and the incidence of fractures in the main trial are presented here.

Methods

Patients and procedures

4724 postmenopausal women with histologically confirmed, completely resected unilateral breast cancer that was oestrogen-receptor positive or of unknown status, who were disease-free after 2–3 years of treatment with tamoxifen, were randomly assigned in a double-blind design to either continue oral tamoxifen 20 mg/day or switch to oral exemestane 25 mg/day to complete a total of 5 years of adjuvant endocrine therapy. Randomisation was done through the local data centre for each cooperative group or via the International Cancer Collaborative Group (ICCG) Coordinating Data Centre.

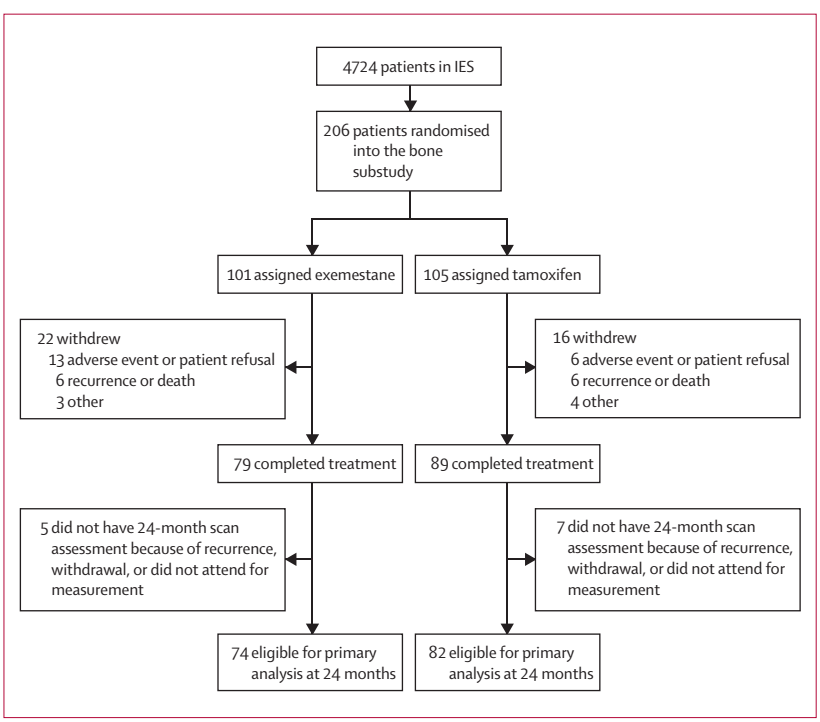

Figure 1: **Trial profile**

The ICCG Coordinating Data Centre prepared the randomisation scheme by computer-generated permuted blocks of eight patients, stratified according to centre. The trial identification numbers in each block were randomly shuffled to avoid consecutive allocation. Priority was given to the main trial, therefore the bone subprotocol was started later than the main protocol, and was implemented in 17 of the 366 centres involved in the overall study that had access to high-quality, dedicated, dual-energy X-ray absorptiometry (DXA) bone densitometry facilities. The institutional review board or local ethics committee at each participating centre approved the subprotocol, and all patients gave written informed consent to participate.

Patients taking part in the main study at the 17 centres and who were eligible for the bone substudy were invited to take part in the substudy. Eligibility criteria were: eligible for the main study;[3] no evidence of osteoporosis according to lumbar spine (L1–4) and total hip BMD T scores (above –2·5 SD; ie, not osteoporotic); no current bisphosphonate treatment or use in the previous 6 months; no other selective oestrogen-receptor modulator, hormone-replacement therapy, or calcium supplements for longer than 1 month in the previous 6 months; no fragility or non-fragility fractures in the previous 6 months; long-term accurate determination of BMD by DXA technically possible; and no other disease or concomitant drug treatment with expected effects on bone metabolism.

BMD was measured by DXA of lumbar spine (L1–4) and the hip (total, femoral neck, and Ward's triangle) before randomisation into the IES and at 6 months, 12 months, and 24 months. Further BMD measurements at the end of treatment and at 1 year and 2 years after completion are still in progress. To improve precision and provide consistency, DXA scanning procedures were standardised and the scans were monitored and centrally analysed according to the study protocol by the Central Evaluation Facility at the Department of BioSurgery and Surgical Technology, Imperial College, London, UK. Before and throughout the study, instrument quality-control procedures were undertaken by the different scanning centres, and included quality-assurance scans defined in the manufacturer's operating manual and twice-weekly scans of the manufacturer's spine phantom. These results were reviewed on a regular basis by the Central Evaluation Facility to confirm that the equipment was working within specifications and no major fluctuations were occurring that might affect the accuracy of the final DXA result.

Serum and urine samples were collected for analysis of biochemical markers of bone turnover on two occasions before randomisation to provide a reliable baseline assessment and at months 3, 6, 9, 12, 18, and 24 on study treatment. The bone markers assessed were the resorption markers urinary N-telopeptide (NTX), deoxypyridinoline, and serum C-terminal cross-linked

telopeptide of type 1 collagen (CTX); and the formation markers serum bone alkaline phosphatase, osteocalcin, and C-terminal procollagen peptide fragment (PICP). All markers were measured at the Francis Fraser Laboratory (Clinical Pathology Accreditation [UK] Ltd certified) at the Hammersmith Hospital, London, UK, under the supervision of one investigator (SIG), and internal quality-control samples of high, medium, and low concentrations were processed with each batch of serum samples. Serum was taken, whenever possible, in the fasting state, and at a similar time of day to minimise diurnal and diet-related effects on bone markers. The second voided urine of the day was collected for measurements of urinary markers, and the results were expressed as a ratio to urinary creatinine concentration. Bone markers were measured by ELISA. The coefficients of variation within and between assays were less than 8·4% for all markers.

Fracture incidence was recorded throughout the study, and spinal fractures were assessed by the Central Evaluation Facility on lateral thoracic and lumbar spine radiographs taken locally with central assessment before randomisation, at the end of treatment, and 2 years after the end of treatment. In the IES, fractures were reported on a case report form at each follow-up. However, routine radiographs of the spine were not done in the main study and, therefore, asymptomatic spinal fractures were typically not identified.

Each person is counted once in an incident case analysis, with their worse graded event over follow-up being the one that is counted. Since the safety data was Medical Dictionary for Regulatories Activities (MedDRA) coded, the fracture MedDRA codes were combined to create an overall group. Each person was counted once (even, for example, when the patient has had a hip and spine fracture at different times during follow-up) and also where each MedDRA code was considered separately, so the number reporting hip, spine, wrist and other are not exclusive.

The primary endpoint of the substudy was mean annual change from baseline in lumbar spine and total hip BMD in patients who remained on tamoxifen, compared with that in participants who switched to exemestane. Secondary endpoints included changes in markers of bone turnover between the two treatment groups at each timepoint, within-group changes in BMD and bone markers, and assessment of the links between changes in biochemical markers of bone metabolism and changes in BMD. The incidences of fractures in the IES treatment groups were also assessed.

	Exemestane (n=101)	Tamoxifen (n=105)
Mean (SD) BMD, g/cm²		
Lumbar spine	1·1 (0·2)	1·1 (0·2)
Total hip	1·0 (0·1)	1·0 (0·1)
Mean (SD) T score		
Lumbar spine	−0·6 (1·1)	−0·5 (1·1)
Total hip	−0·2 (1·0)	−0·1 (1·0)
Osteopenia* (%)		
Lumbar spine	42 (42)	37 (35)
Total hip	23 (23)	21 (20)
Either site	49 (49)	46 (44)

*WHO criteria for osteopenia (T score <−1·0 and >−2·5).

Table 1: **Baseline BMD (prerandomisation)**

Statistical analysis

The sample size for this substudy was based on predicted differences in BMD from studies of tamoxifen in postmenopausal women.[14] 172 participants were needed to detect a conservative estimated 2% difference in BMD (SD 4) between treatment groups at 24 months, with 90% power and a two-sided significance level of 0·05. The planned participant number was rounded up to 200 participants to allow for dropouts. The study has 89% power based on the number of patients who completed the study and 87% for the number of patients with BMD results available at 24 months.

Analyses were done on all cleaned data processed by the Central Evaluation Facility available on Nov 8, 2005, by use of Stata (version 8.2). The primary analysis was

	Median (IQR) at baseline		Median (IQR) at 24 months	
	Exemestane (n=99)	Tamoxifen (n=104)	Exemestane (n=99)	Tamoxifen (n=104)
Resorption				
Deoxypyridinoline*	5·4 (4·8–6·4)	5·9 (4·9–7·3)	7·5 (5·8–9·2)	5·4 (4·2–7·4)
NTX*	42·7 (35·2–53·5)	40·9 (30·3–59·5)†	79·1 (50·1–100·7)	43·4 (32·6–58·7)†
CTX (pmol/L)	2170·0 (1571·0–3057·0)	2696·0 (2007·5–3561·5)†	4639·0 (3138·0–5862·0)	2174·5 (1413·5–3489·0)†
Formation				
Bone alkaline phosphase (U/L)	24·5 (19·0–29·1)	23·7 (18·7–28·6)‡	37·4 (31·0–47·5)	23·90 (19·8–32·5)‡
Osteocalcin (µg/L)	10·3 (7·9–14·1)	11·4 (8·1–14·9)†	20·8 (17·2–25·9)	9·7 (7·5–14·0)†
PICP (µg/L)	82·8 (69·9–102·6)	85·7 (71·4–101·9)‡	110·4 (82·8–132·0)	94·2 (73·2–109·2)‡

Data are means of prerandomisation and baseline samples. *Given as ratio to urinary creatinine. Data missing for one† or two‡ patients for these markers.

Table 2: **Baseline biochemical markers**

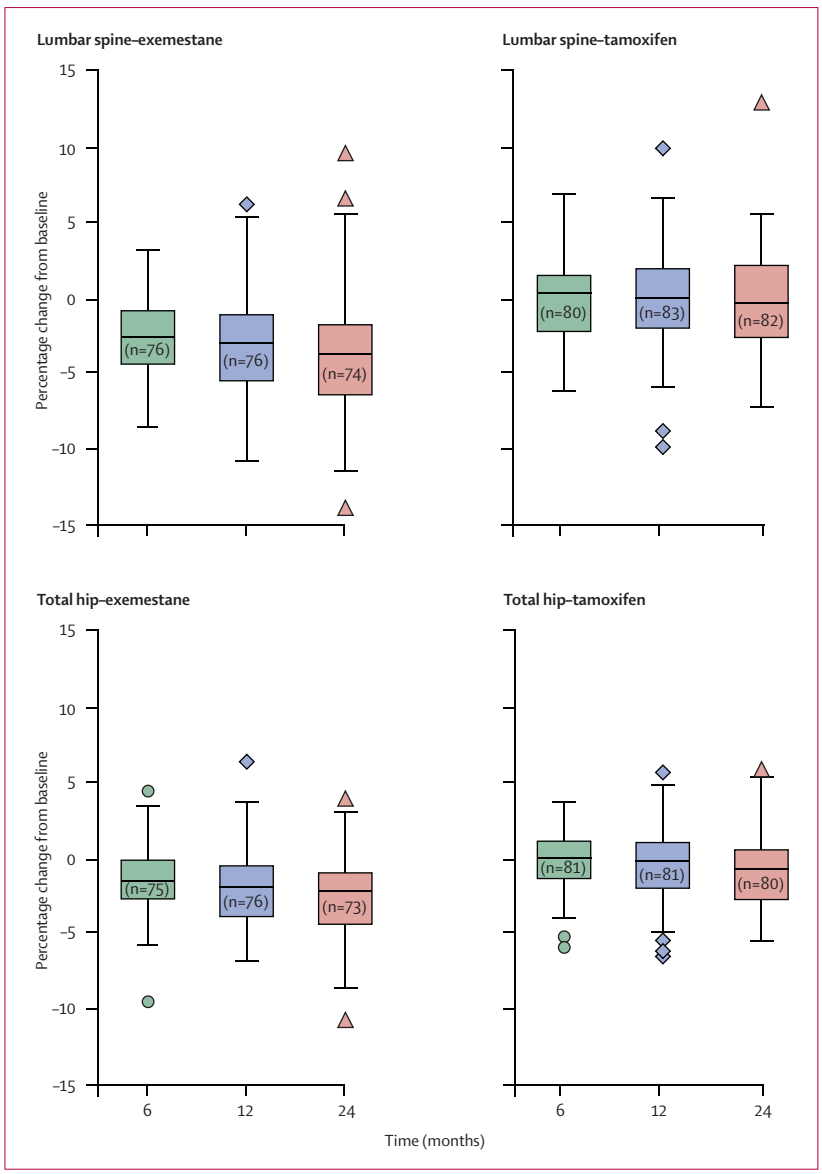

Figure 2: **Percentage BMD change from baseline (median and IQR) at lumbar spine and total hip**

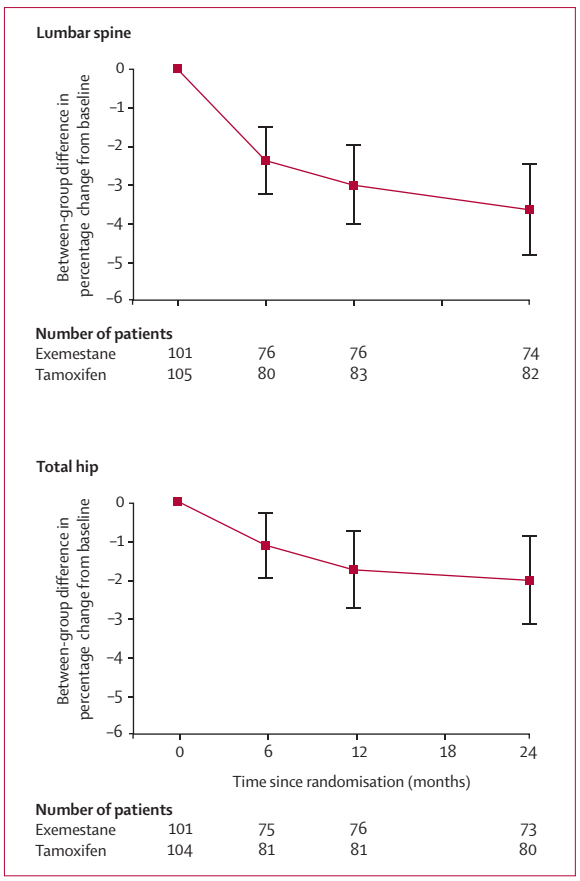

Figure 3: **Difference in mean percentage change from baseline BMD (with 95% CIs) between the exemestane and tamoxifen treatment groups at lumbar spine and total hip**

based on treatment actually received for all treated patients, with data within predefined visit windows of 1 month before or after the follow-up date for the visits at months 3, 6, 9, 12, and 18, and within 1 month before or 2 months after the 24-month window to incorporate eligible end-of-treatment visits. Before analysis, a pragmatic definition of when study participants should be censored was established. It included completion of study treatment, the start of any bisphosphonate treatment, and the date of relapse—unless the relapse was a skeletal metastasis, in which case, to minimise confounding effects of bone metastasis on BMD and bone metabolism, patients were censored at a last visit that was at least 3 months before the relapse date. All data in the results section relate to this analysis population unless otherwise stated. Values after censoring are treated as missing in subsequent analyses. Sensitivity analyses at all time points were done to confirm the robustness of the primary analysis and included the intention-to-treat population, randomised treatment, and patients with complete follow-up.

BMD changes at all sites were expressed as percentage changes from baseline and compared by use of two-sample (between-treatment groups) and paired (within groups) *t* tests. Data for the lumbar spine and total hip are reported, but specific measurements for the femoral neck and Ward's triangle BMD are not shown. Absolute changes in T scores were also considered (data not shown).

Because bone markers were not normally distributed, data are given as median (IQR). The Mann-Whitney and Wilcoxon sign rank non-parametric tests were used to compare percentage change from baseline. Absolute values of the bone markers are shown to allow for the effects of 2–3 years of previous treatment with tamoxifen, and to enable comparisons with other trials.

To account for the longitudinal nature of the data, we took a repeated-measures approach using generalised

estimating equations. For these data, an unstructured correlation matrix was assumed. The independent variable was absolute BMD at each time point as a continuous variable. Dependent variables were treatment received, baseline absolute BMD, month of visit (3, 6, 9, 12, 18, and 24), and prespecified covariates of age (<60 years, 60–70 years, >70 years) and weight (<70 kg, 70–80 kg, >80 kg). Interactions between covariates and also polynomial effects were considered. None significantly improved the fit of the models. Also, different correlation structures, such as exchangeable, were used to confirm the models' robustness, along with modelling of the data without the prespecified covariates. Neither of these sensitivity checks affected the results. For simplicity, and to aid clinical interpretation, *t* tests and change from baseline are shown rather than the more statistically powerful but complex longitudinal repeated-measures model.

Fractures were recorded for all patients as adverse events in the main study. To identify the adverse risk associated with these events, they were analysed for a safety population as defined in the main study that included patients according to treatment received, censoring at time of relapse (or 3 months before if the relapse was a skeletal metastasis). Analyses restricted to time on endocrine treatment and all available follow-up (on treatment plus post-treatment follow-up) were done. Incidence rates were analysed by treatment group, per 1000 women-years, and allowed in every case for one fracture per patient and several fractures per patient over all available follow-up. An analysis was done of time to first recorded fracture by use of a Cox proportional hazards model that adjusted for age (<60 years, 60–70 years, >70 years) and country fracture risk (defined as average risk of osteoporotic hip fracture for a country compared with a reference country with a very high risk; very high, high, medium, low).[15] As in the main study, and to account for multiple testing of adverse events, p<0·01 was taken as significant for the fracture data. However, to allow comparison with other trials, 95% CI are quoted here. This study is registered with ISRCTN number 11883920.

Role of the funding source

The pharmaceutical sponsor Pfizer is the parent company of Pharmacia who provided some of the treatments, gave organisational and monitoring support to the Central Evaluation Facility, and was represented on the trial steering committee; the committee was made up of at least two representatives from each of the 20 collaborative groups (local clinical study representative and the senior data manager or statistician), representatives from the Coordinating Data Centre, including the trial manager and study statisticians, and three from the pharmaceutical sponsor. The corresponding author directed all analyses, had full access to all the data in the study, and had final responsibility for the decision to submit the report for publication.

Results

Between April, 2000, and February, 2003, 206 patients (101 assigned exemestane and 105 tamoxifen) from 17 centres were entered into the bone substudy (figure 1). The randomised groups were well balanced in terms of demographics and treatments received before randomisation. At baseline, BMD, T score, and the proportion of osteopenic patients or levels of bone markers did not differ significantly between the groups (tables 1 and 2). 95 patients were osteopenic at baseline (WHO criteria for osteopenia is T score <–1·0 and >–2·5), 49 in the exemestane group and 46 in the tamoxifen group. 74 patients in the exemestane group and 82 in the tamoxifen group had BMA data at 24 months (figure 1).

Figure 2 shows the percentage changes from baseline in BMD at the lumbar spine and total hip for each visit. The data are approximately normally distributed. No statistically significant within-group changes in BMD were seen with continuation of tamoxifen. However, BMD rapidly decreased from baseline in the first 6 months after switching from tamoxifen to exemestane by 0·051 g/cm^3 (2·7%; 95% CI 2·0–3·4; p<0·0001) at the lumbar spine and 0·025 g/cm^3 (1·4%; 0·8–1·9; p<0·0001) at the total hip. Thereafter the decline in BMD progressively slowed in months 6–12 and 12–24, but continued to decline (figure 2). Reductions in BMD were only 1·0% (0·39–1·70; p=0·002) and 0·8% (0·29–1·39; p=0·003) in year 2 at the lumbar spine and hip, respectively, between 12 and 24 months. The differences in mean BMD, with 95% CI between the treatment groups at each time point (figure 3) again show the rapid changes in BMD in the first 6 months after switching from tamoxifen. These findings are consistent with the point estimates and statistical precision provided by the

	Exemestane (n=2320)	Tamoxifen (n=2338)
Hip	14	9
Spine	14	5
Wrist	25	30
Other	116	80
Osteoporotic	19	19

Table 3: **Incidence and type of fractures during follow-up**

	Exemestane (n=101)		Tamoxifen (n=105)	
	Non-osteopenic at baseline (n=52)	Osteopenic at baseline (n=49)	Non-osteopenic at baseline (n=59)	Osteopenic at baseline (n=46)
Non-osteopenic and non-osteoporotic at 24 months	34	0	46	4
Osteopenic at 24 months	8	36	3	38
Osteoporotic at 24 months	0	5	0	0
24 month data unavailable*	10	8	10	4

*Data not available because of withdrawals (see figure 1) and missing.

Table 4: **Transition between normal, osteopenic, and osteoporotic bone health after 24 months**

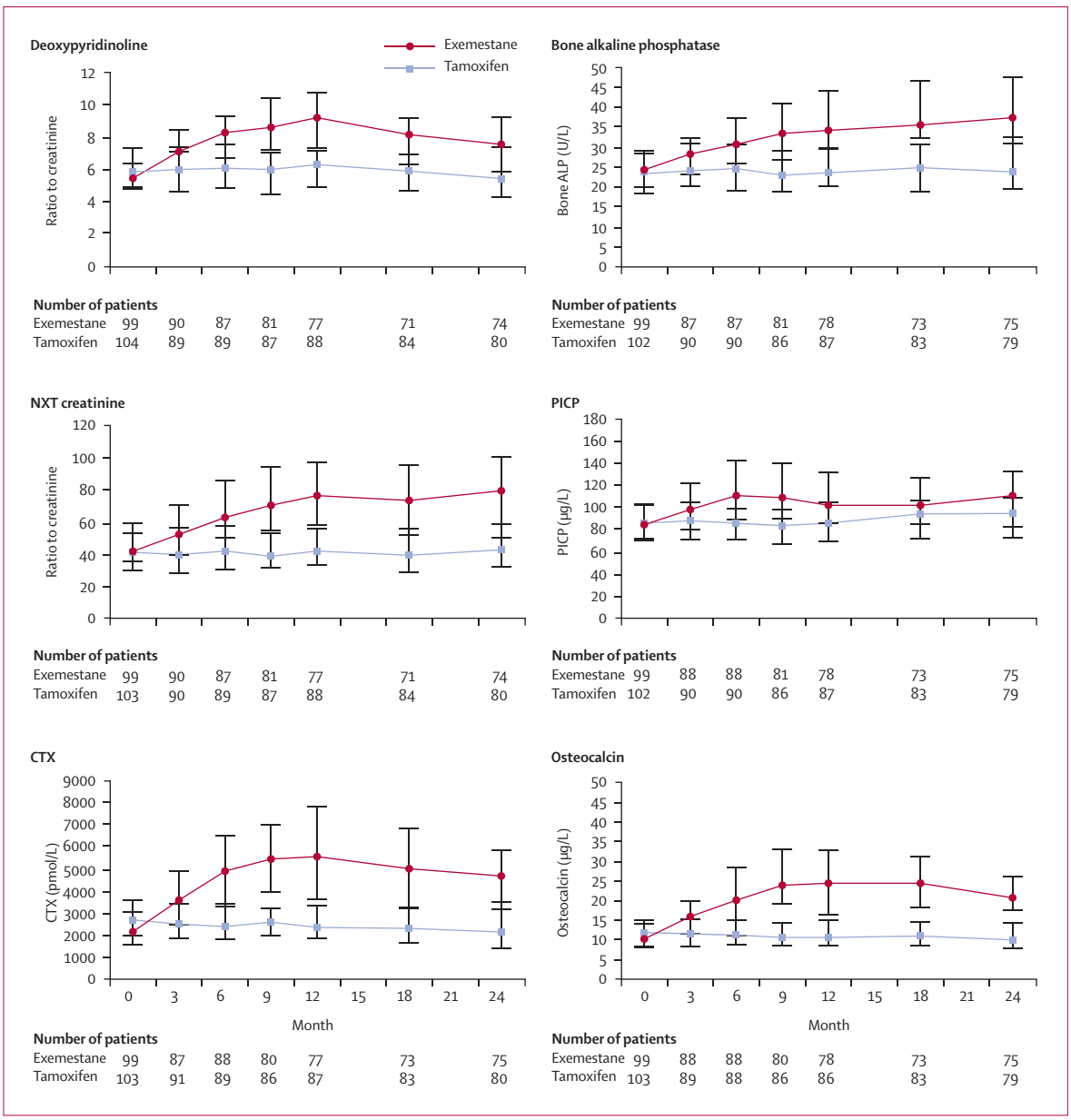

Figure 4: **Median (IQR) changes in bone resorption and formation markers**

generalised estimating equation approach used to model the longitudinal data (data not shown). The numbers and types of fractures during follow-up are shown in table 3.

The decline in BMD after the switch to exemestane resulted in a greater incidence of osteopenia at 24 months, and five patients—who were osteopenic at baseline—developed osteoporosis (table 4).

The changes in bone markers from baseline (absolute and percentage changes) were statistically significantly different between treatments at all time points (figure 4). Bone resorption and formation marker measurements remained fairly constant over time in the tamoxifen group. Withdrawal of tamoxifen associated with the start of exemestane increased the rate of bone turnover. The greatest changes were recorded during the first 6 months. In the exemestane group, resorption marker measurements were highest at 12 months, and then decreased—but remained higher than that of the tamoxifen group at 24 months—while bone formation markers peaked between 18 and 24 months. The proportion of patients who had concentrations of bone markers within the normal ranges at baseline and went on to have values outside the normal range was significantly higher in the exemestane group than in the tamoxifen group; for example, 81 (82%) of patients assigned exemestane had increases in the bone resorption

	Fracture incidence rates per 1000 women-years (95% CI) (one fracture per patient)		Fracture incidence rates per 1000 women-years (95% CI) (several fractures per patient)	
	Exemestane	Tamoxifen	Exemestane	Tamoxifen
Intention-to-treat	17·6 (15·1–20·4)	13·2 (11·1–15·6)	20·1 (17·5–23·0)	16·0 (13·8–18·7)
As treated, all events, censoring at relapse	17·1 (14·7–20·0)	12·3 (10·2–14·7)	19·2 (16·6–22·1)	15·1 (12·8–17·7)
As treated, on treatment events, censoring at relapse	16·7 (13·7–20·3)	11·9 (9·5–15·0)	18·5 (15·4–22·3)	13·7 (11·0–16·9)

Table 5: **Fracture incidence rates per 1000 women-years over all follow-up from the main study**

marker deoxypyridinoline versus 50 (49%) of those receiving tamoxifen (p<0·001), and increases in the formation marker bone alkaline phosphatase were recorded in 81 (82%) and 38 (37%) of patients assigned exemestane and tamoxifen, respectively (p<0·001). Similar changes were recorded for the other bone resorption and formation markers assessed.

Generally, there were significant negative correlations between bone-marker and BMD changes. Significant, albeit weak, correlations between bone-marker and BMD changes at 24 months (r=–0·172 to –0·343) compared with those at baseline were recorded for all bone markers, with the exception of PICP for the spine, and PICP and deoxypyridinoline for the hip.

In the main study, which had a median follow-up in all participants of 58 months (range 0–89·7) and median exposure to exemestane of 30 months (IQR 24·4–34·3), 162 (7%) of patients in the exemestane group had fractures compared with 115 (5%) patients in the tamoxifen group (odds ratio 1·45 [1·13–1·87]; p=0·003, by safety analysis); 84 (4%) and 64 (3%; 1·33 [0·95–1·89]; p=0·086) of these patients had these fractures before the follow-up visit at 24 months. The incidences of multiple fractures per 1000 women-years of observation (safety analysis and all events) were 19 (17–22) and 15 (13–18) for the exemestane and tamoxifen groups, respectively (table 5). Although age and country fracture risk[15] affected fracture risk in univariate testing, a Cox proportional hazards analysis that took into account time to first fracture and adjusted for these factors did not significantly change the risk of fracture according to treatment group (data not shown).

The number of fractures over 24 months was low, and no conclusions on relation to BMD or bone-marker changes can be made. Nine (4%) fractures occurred in total, of which three (1%) were traumatic and six (3%) were due to fragility (three in each treatment group).

Discussion

We investigated the possible effects on bone health of the steroidal aromatase inhibitor exemestane, coupled with previous treatment with tamoxifen compared with the effects of remaining on tamoxifen. We postulated that pretreatment with tamoxifen, coupled with the possible anabolic effects of exemestane, would lead to fewer adverse effects on bone than have been reported for treatment with a non-steroidal aromatase inhibitor alone. Although significant changes in bone markers and BMD were recorded within 6 months of tamoxifen withdrawal and exemestane initiation, these are due, at least partly, to the cessation of bone-turnover suppression induced by tamoxifen. The percentage median rates of lumbar spine bone loss for this group in the IES were –2·9%, –3·6%, and –4·0% at 6, 12, and 24 months, respectively. In the MA-17 study of extended adjuvant therapy with letrozole versus placebo after 5 years of tamoxifen treatment, a 3% decline in lumbar spine BMD after 12 months was measured in the placebo group on withdrawal of tamoxifen, followed by recovery to +1% at 24 months.[16] The BMDs in the population treated with letrozole were –2·9% at 12 months and –5·4% at 24 months.

We have not encountered a patient with normal baseline BMD (T score >–1) who developed osteoporosis. Although our sample size is quite small, such an event would be highly unlikely because bone loss of more than 12–15% would be necessary for transition from a healthy to osteoporotic state—a degree of change that was not seen in any patient. Even with 5 years of treatment with anastrozole, osteoporosis in a patient with baseline BMD has not been reported.[17]

Another study that investigated the skeletal effects of exemestane is a placebo-controlled trial in 128 Scandinavian women who had very low-risk breast cancer.[18] In that study, the annual reduction in spinal BMD did not differ significantly between women assigned exemestane and those assigned placebo (2·2% *vs* 1·8%; p=NS). However, annual changes in hip BMD did differ between the two treatment groups (2·7% *vs* 1·5%; p=0·024). The changes in the placebo group were greater than might be expected, perhaps due to previously unrecognised vitamin D deficiency in this Nordic population.[19] The differences between the two groups were generally similar to those recorded in the second year of the IES bone study, once the effects of tamoxifen withdrawal had waned.

In studies reported to date, fracture rates with non-steroidal aromatase inhibitors have been consistently higher than with tamoxifen. In the ATAC study[1]—which had a median follow-up of 68 months—the incidence of fractures was 340 (11%) with anastrazole compared with only 237 (8%) with tamoxifen (odds ratio 1·49 [95% CI 1·25–1·77]; p<0·0001). Similarly, in the BIG 1-98 study 2 (median follow-up 36 months), the fracture rate with letrozole (211; 9%) was about 40% higher than that with tamoxifen (141; 6%).[20] In the IES, the incidence of fractures increased numerically during exemestane

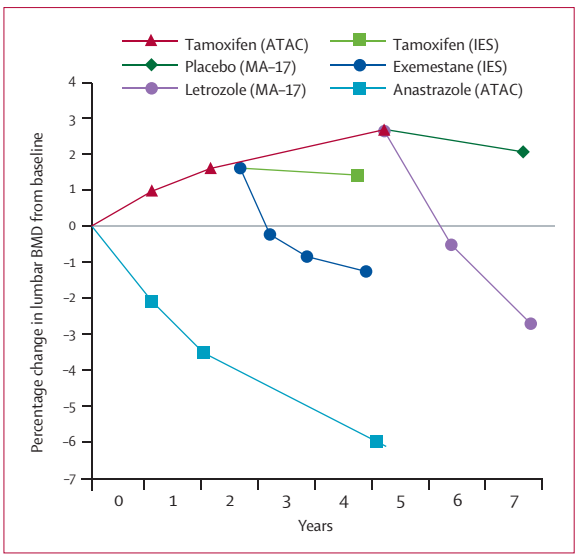

Figure 5: **Estimated changes in lumbar-spine BMD over 5 years with tamoxifen for 5 years; anastrozole for 5 years; the IES tamoxifen-exemestane switch strategy; and tamoxifen for 5 years followed by either letrozole or placebo**

Adapted from data presented from the ATAC bone subprotocol data at the American Society of Clinical Oncology Conference 2006[10] and Perez and colleagues.[16]

treatment (median duration 30 months) and became significant (7% *vs* 5%; p≤0·01) when all events were counted during both the treatment and follow-up periods (median duration 58 months). A Cox proportional hazards analysis showed a hazard ratio of 1·27 (1·03–1·58) in the hazard for fracture in all analyses, with no significant effect of bodyweight, country of residence, or age on the risk of fractures (data not shown). The incidence of fractures in the exemestane group was 19·2 per 1000 women-years. In the ATAC and BIG 1-98 trials, the annual fracture incidences in women receiving anastrozole or letrozole were slightly higher at 21·6 and 22·0 per 1000 women-years, respectively. Correspondingly, the fracture incidence per 1000 women-years with tamoxifen alone in the IES (15) was similar to that reported for women randomly assigned tamoxifen in the ATAC (13) or BIG 1-98 (15) trials.[2,17] The difference in fracture incidence between the two treatment groups in IES was of similar magnitude to the 1·29 hazard ratio with tamoxifen compared with placebo in women aged over 50 years reported in the P1 breast cancer prevention study.[8] These observations suggest that the excess fracture incidence associated with exemestane is related as much to the absence of tamoxifen as to the use of exemestane.

In this study, we assessed bone markers of resorption and formation. Assessment of the marker changes is confounded by previous treatment with tamoxifen, which caused a reduction in bone turnover. The changes in bone markers in the ATAC trial suggest that bone resorption and formation at the time of randomisation were probably suppressed by about 30% and 15%, respectively, compared with an untreated population.[21] Therefore, assessment of percentage changes in bone markers in the IES gives a falsely high impression of the effects of exemestane on bone turnover. In terms of absolute values, the changes in bone markers were modest, with effects on bone resorption reaching a maximum within the first 6 months. Because of the expected coupling of osteoclast and osteoblast function, the increases in bone formation markers continued for 12 months, but remained constant thereafter.

The IES has shown an advantage in terms of preventing breast cancer recurrence for the switch to exemestane after 2–3 years of tamoxifen compared with continuing tamoxifen.[13] The bone subprotocol results reported here indicate that this advantage is achieved at the expense of some detriment to skeletal health (4·0% bone loss at the lumbar spine after 2 years with exemestane *vs* 0·6% with tamoxifen). Figure 5 summarises the lumbar-spine BMD results from this study superimposed on the expected BMD increase with 2–3 years of previous treatment with tamoxifen and the BMD data from the ATAC and MA-17 bone subprotocols. Although this is a comparison of different datasets, the probable effect of the different aromatase inhibitor treatments on bone health can be estimated. The overall 5-year effects on BMD of 2–3 years of treatment with tamoxifen followed by exemestane for 2–3 years are modest, but the rates of demineralisation on exemestane, letrozole, and anastrazole seem to be comparable during the first 2 years of treatment.

We recommend that in monitoring of patients receiving tamoxifen followed by exemestane, a BMD assessment in accordance with the American Society of Clinical Oncology recommendations should be done around the time of switching treatment.[22] Patients with BMD in the normal range at this time do not need further BMD assessment, but should be given lifestyle advice on preservation of bone health and encouraged to take adequate calcium and vitamin D through the diet or supplements. Those with osteopenia should have BMD measurements every 1–2 years, lifestyle advice, calcium and vitamin D supplementation, and therapeutic intervention with a bisphosphonate as appropriate. Patients with pre-existing osteoporosis should also receive bisphosphonate treatment. However, no data exist on BMD changes in patients with pre-existing osteoporosis for any of the aromatase inhibitors. An assumption is made that bisphosphonates will be effective treatment for osteoporosis in the presence of an aromatase inhibitor, but specific data in this subgroup of women are needed before precise recommendations can be made.

In conclusion, these results indicate that the IES switch strategy of replacing tamoxifen after 2–3 years with exemestane for a further 2–3 years leads to reversal of the protective effect of tamoxifen on bone.

Contributors

REC, LMB, SMG, EH, JMB, and RCC developed the protocol. REC, LMB, SMG, LK, JMB, and RCC took part in writing the report. REC managed the steering committee and took part in interpretation of data. LMB provided and analysed the BMD data and fracture incidence, supervised and quality controlled BMD measurements, and managed the study. SMG provided and supervised data on biochemical bone markers. LK, EH, and JMB did the statistical analysis. EV, JNF, SC, and AP collected data. EV, JNF, SC, AP, CS, and EH reviewed and approved the report. CS coordinated the main trial. RCC calculated the CIs for the main trial and took part in interpreting data.

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Acknowledgments

We thank J Heer, J Liao, D Price (Central Evaluation Facility); G Baffoe, S Niththyananthan (Bone Markers Unit); I Amoako, L Gibson (Coordinating Data Centre) of Imperial College London, UK; Pfizer for their support and funding; the Independent Data Monitoring Committee (IDMC); and especially, the women who participated in this study.

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