Effects of exemestane and tamoxifen on bone health within the Tamoxifen Exemestane Adjuvant Multicentre (TEAM) trial: results of a German, 12-month, prospective, randomised substudy

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Background: Adjuvant treatment of hormone receptor-positive breast cancer in postmenopausal women with aromatase inhibitors may be associated with increased bone loss.

 Patients and methods: Two hundred patients were randomised to receive exemestane or tamoxifen as adjuvant treatment of hormone receptor-positive breast cancer. Bone mineral density (BMD) was assessed by dual-energy X-ray absorptiometry at baseline and after 6 and 12 months treatment.

Results: One hundred and sixty-one patients were assessable. Tamoxifen treatment resulted in a 0.5% increase from baseline in BMD at the spine, which was maintained at 12 months. Exemestane-treated patients experienced a 2.6% decrease from baseline in BMD at the spine at 6 months and a further 0.2% decrease at 12 months. There were significant differences in the changes in BMD between tamoxifen and exemestane at 6 and 12 months (P = 0.0026 and P = 0.0008, respectively). The mean changes in BMD from baseline at the total hip were also significantly different between exemestane and tamoxifen at 6 and 12 months (P = 0.0009 and P = 0.04, respectively). There was no difference between tamoxifen and exemestane in mean changes in BMD from baseline at the femoral neck.

Conclusions: Exemestane treatment resulted in an increase in bone loss at 6 months; bone loss stabilised after 6- to 12-month treatment.

Key words: aromatase inhibitor, bone mineral density, early breast cancer, exemestane, fracture, osteoporosis

Introduction

Third-generation aromatase inhibitors (AIs), which include exemestane, anastrozole and letrozole, are replacing tamoxifen as adjuvant therapy for postmenopausal women with hormone receptor-positive early breast cancer (EBC) due to the superior efficacy shown in several recent head-to-head trials [1–7].

AIs have a different mechanism of action from tamoxifen and, as a result, a different safety profile. Tamoxifen is associated with prevention of bone loss in postmenopausal patients [8], but has also been shown to increase the risk of thromboembolic events and endometrial cancer [9]. In contrast, AIs have been associated with an accelerated decrease in bone mineral density (BMD) and increased fracture risk and osteoporosis [1, 3, 4, 7, 10]. The effects of AIs on BMD should, however, be considered in the context of the other benefits of AIs relative to tamoxifen. Bone mineral loss associated with AIs is not life threatening and can be effectively managed with lifestyle advice, vitamin D supplementation and the use of bisphosphonates [11].

The Tamoxifen Exemestane Adjuvant Multicentre (TEAM) trial is a phase III, randomised, parallel-group, multicentre trial organised as a single reporting entity, consisting of separately managed, country-specific trials in nine participating countries. The TEAM trial was originally designed to compare the efficacy and safety of 5 years of adjuvant exemestane versus 5 years of tamoxifen in postmenopausal women with EBC. Following the results of the Intergroup Exemestane Study (IES) [7], the TEAM study was amended to assess 5 years of adjuvant exemestane compared with 2.5 years of tamoxifen followed by 2.5 years of exemestane. The co-primary objectives of the TEAM trial are to compare disease-free survival associated with the two treatments at 2.75 and 5 years.

Here, we describe results from a prospective, open-label, randomised, multicentre, German bone substudy of the TEAM...
trial. Previous studies with AIs have shown that the rate of bone loss is more rapid during the first year of treatment and appears to slow and stabilise after this initial period [12, 13]. Therefore, this substudy was designed to compare the effects of exemestane and tamoxifen on BMD during the first year of adjuvant treatment of postmenopausal women with estrogen receptor (ER)-positive EBC.

patients and methods

All patients provided written, informed consent before enrolling into the study. The study was approved by the local ethics committees and was conducted in accordance with the Declaration of Helsinki.

study design

This was an open-label, randomised, multicentre German substudy of the TEAM trial that was designed to compare the effects of exemestane and tamoxifen on BMD in postmenopausal women with ER-positive breast cancer. Patients were randomised to receive either exemestane for 5 years or tamoxifen for 2.5–3 years followed by exemestane for 2–2.5 years, for a total of 5 years endocrine therapy. Randomisation was carried out for each centre in blocks of six patients to exemestane or tamoxifen in order to achieve a balanced 1 : 1 randomisation at all centres. Here, we report a 12-month analysis of the effects of exemestane or tamoxifen on BMD, which was the primary end point of the substudy. Therefore, the amended study design of the TEAM trial, with the switch to exemestane after 2.5–3 years of tamoxifen, does not affect our substudy.

The study recruited postmenopausal women who had stage I, II, IIB and IIIA T1–3, N0–2, M0, ER-positive and/or progesterone (PR)-positive breast cancer and who were candidates for adjuvant endocrine therapy. Patients were required to have completed primary surgery and/or radiotherapy and/or chemotherapy, if indicated, in accordance with local guidelines, to have adequate renal, hepatic and haematological function and an Eastern Cooperative Oncology Group performance status of zero to two [14]. A T score >2.5 [dual X-ray absorptiometry (DXA)] and abstinence from strenuous exercise and alcohol consumption during the 48-h period before each study visit were also required.

Patients were excluded if they had cancer that could not be completely resected with negative margins or met one of the following criteria: inflammatory breast cancer, histologically positive supraclavicular nodes, local skin ulceration/infiltration, neoadjuvant chemotherapy, ER and PR-negative primary tumour or ER/PR unknown status or evidence of distant metastasis. Patients receiving hormonal therapy as adjuvant therapy for prior breast cancer, or with uncontrolled cardiac disease, other significant malignancies within the past 3 years or other serious illnesses, were also excluded from the study. Other exclusion criteria were diseases that require chronic intake of drugs that interfere with bone metabolism (e.g. glucocorticosteroids, antiepileptics, bisphosphonates, selective ER modulators, strontium ranelate, teriparatide, calcitonin, fluoride and vitamin K antagonists) and metabolic diseases that affect bone metabolism and/or require treatment (e.g. primary hyperparathyroidism).

treatment

Patients received oral treatment with either tamoxifen 20 mg once daily or exemestane 25 mg once daily. No dose escalations, reductions or modifications were permitted. However, discontinuation of treatment was permitted due to patient withdrawal of consent, if the investigator considered it was medically necessary, unacceptable toxicity or relapse of disease. Fracture or development of osteoporosis (T score < −2.5) led to withdrawal from the bone substudy only. All patients continued to be followed up for survival, whether or not they discontinued treatment prematurely.

Adjuvant hormonal treatment was initiated within 14 weeks after completion of surgery. Patients were required to complete a ‘Drug Administration Record’ at home, which was brought to each clinic visit to document treatment compliance.

BMD measurements

BMD was assessed at baseline and after 6 and 12 months of treatment. Assessments of BMD were carried out using DXA imaging at the lumbar spine (L1–L4), neck of femur and total hip.

Osteoporosis-related risk factors and clinical signs and symptoms were also evaluated by an osteoporosis-related questionnaire at the start of the study [15]. The clinical fracture rate was assessed and in case of a bone fracture, scintigraphy was carried out and the cause of the fracture was documented with a questionnaire. Any osteoporosis-related fracture led to study withdrawal.

primary end point

The primary end point was change in BMD (g/cm²) on treatment from baseline to month 12 in lumbar spine (integral of L1–L4) for exemestane or tamoxifen.

secondary end points

Secondary end points included the change in BMD (g/cm²) on treatment from baseline to month 6 in lumbar spine (integral of L1–L4) for exemestane or tamoxifen; the changes from baseline to months 6 and 12 in standardised BMD (T scores and Z scores) in lumbar spine (L1–L4); the change in BMD (g/cm² and standardised as T scores and Z scores) from baseline to months 6 and 12 in each of the lumbar vertebrae L1, L2, L3 and L4 and changes from baseline to months 6 and 12 in BMD (g/cm² and standardised as T scores and Z scores) in the femoral neck and total hip. The difference in fracture rate between tamoxifen and exemestane and the possible effects of demographic data, clinical baseline and medical history factors on changes in BMD were also assessed.

statistical analysis

Due to a lack of appropriate historical data, formal sample size estimation was not carried out. A total of 120 assessable patients (60 patients per treatment group) were considered sufficient for the exploratory 12-month evaluation. A total of 200 patients were randomised to achieve these numbers.

The intent-to-treat (ITT) population included all patients who were randomised to the bone substudy and had a baseline assessment and at least one postbaseline measurement for BMD; the ITT population was used for all analyses. Results were reported as absolute BMD values (g/cm²) and as standardised T and Z scores.

The treatments were compared using an analysis of covariance on the changes from baseline to 6 and 12 months in BMD parameters. The treatment group was the class variable and the baseline value was the covariate at a significance level of 0.05.

All database management and statistical analyses were carried out using the Statistical Analysis System version 9.1.

results

patient characteristics

A total of 200 patients registered from August 2004 to August 2006 at nine participating institutions in Germany were
randomised to receive tamoxifen \((n = 103)\) or exemestane \((n = 97)\).

A total of 39 patients were excluded from the ITT population because they did not have an evaluable postbaseline measurement of BMD. Therefore, 161 patients were available for the ITT analysis (tamoxifen \(n = 83\), exemestane \(n = 78\); Figure 1).

Patients’ baseline characteristics are shown in Table 1. The groups were well balanced with respect to demographics and previous treatments.

**primary end point**

**mean change from baseline in BMD: lumbar spine at 12 months.** The percentage mean change in spinal BMD \((g/cm^2)\) from baseline for tamoxifen was 0.5% at 12 months (Figure 2). In contrast, the percentage mean change in spinal BMD \((g/cm^2)\) from baseline for exemestane was −2.8% at 12 months (Figure 2).

The mean change from baseline in BMD at the lumbar spine was significantly different between tamoxifen and exemestane at 12 months \((P = 0.0008)\).

**secondary end points**

**mean change from baseline in BMD: lumbar spine at 6 months.** The percentage mean change in spinal BMD \((g/cm^2)\) from baseline for tamoxifen was 0.5% at 6 months and no further change was seen at 12 months (Figure 2).

The percentage mean change in spinal BMD \((g/cm^2)\) from baseline for exemestane was −2.6% at 6 months, decreasing to −2.8% at 12 months (Figure 2).

There was a significant difference between tamoxifen and exemestane at 6 months with respect to changes in BMD at the lumbar spine \((P = 0.0026)\).

The BMD results for \(T\) scores and \(Z\) scores in the lumbar spine at 6 and 12 months showed a similar pattern to the changes in BMD (Figure 3; \(Z\) scores not shown). In addition, the BMD results for individual lumbar regions were similar at 6 and 12 months (data not shown).

**mean changes from baseline in BMD: neck of femur at 6 and 12 months.** The percentage mean change in femoral neck BMD \((g/cm^2)\) from baseline for tamoxifen was 0.1% at 6 months and −1.8% at 12 months (Figure 4). The percentage mean change in femoral neck BMD \((g/cm^2)\) from baseline for exemestane

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**Figure 1.** Patient disposition.

**Table 1.** Baseline characteristics

<table>
<thead>
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<th>Variable</th>
<th>Tamoxifen ((n = 83))</th>
<th>Exemestane ((n = 78))</th>
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<td>Mean</td>
<td>SD</td>
<td>Mean</td>
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<tr>
<td>Age (years)</td>
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<td>61.0 7.1</td>
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<td>Height (m)</td>
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<td>163.1 6.0</td>
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<td>Weight (kg)</td>
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<td>70.5 11.2</td>
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<td>27.4 5.4</td>
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<td>L1–L4 BMD (g/cm²)</td>
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<td>1.10 0.15</td>
</tr>
<tr>
<td>BMD ((T) score)</td>
<td>−0.37 1.41</td>
<td>−0.66 1.23</td>
</tr>
<tr>
<td>BMD ((Z) score)</td>
<td>0.63 1.34</td>
<td>0.50 1.33</td>
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<tr>
<td>Neck of femur BMD (g/cm²)</td>
<td>0.91 0.17</td>
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<tr>
<td>BMD ((T) score)</td>
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<td>−0.59 0.98</td>
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<td>BMD ((Z) score)</td>
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<td>Total hip BMD (g/cm²)</td>
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<td>0.99 0.13</td>
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<td>BMD ((T) score)</td>
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<td>0.08 1.02</td>
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<tr>
<td>BMD ((Z) score)</td>
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<td>1.05 1.61</td>
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<tr>
<td>n %</td>
<td>n %</td>
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<td>Prior chemotherapy</td>
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<td>2 2.4</td>
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<tr>
<td></td>
<td>Prior fracture</td>
<td>13 15.7</td>
</tr>
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Descriptive statistics using a t-test showed that there were no differences between the treatment groups regarding BMD variables at baseline. SD, standard deviation; BMI, body mass index; BMD, bone mineral density.
was 2.1.4% at 6 months. However, at 12 months, patients receiving exemestane had experienced an increase from baseline in BMD at the femoral neck of 0.3% (Figure 4).

The mean changes in BMD from baseline at the femoral neck were not significantly different between the exemestane and tamoxifen groups at either 6 months ($P = 0.109$) or 12 months ($P = 0.414$).

The absolute mean change in femoral neck $T$ score from baseline for tamoxifen was $-0.01$ at 6 months and $-0.14$ at 12 months (Figure 5). In the exemestane group, the absolute mean change in femoral neck $T$ score from baseline was $-0.10$ at 6 months and $-0.14$ at 12 months (Figure 5). The BMD results for $Z$ scores showed a similar pattern (data not shown).

mean changes from baseline in BMD: total hip at 6 and 12 months. Patients receiving tamoxifen experienced an increase from baseline in total hip BMD (g/cm$^2$) of 1.5% at 6 months and 0.4% at 12 months (Figure 6). In contrast, the percentage mean change in total hip BMD (g/cm$^2$) from baseline for exemestane was $-1.8\%$ at 6 months, decreasing to $-2.2\%$ at 12 months (Figure 6).

The mean changes from baseline in BMD at the total hip were significantly different between tamoxifen and exemestane at both 6 and 12 months ($P = 0.0009$ and $P = 0.04$, respectively).

The BMD results for $T$ scores and $Z$ scores at 6 and 12 months showed a similar pattern to the changes in BMD (Figure 7; $Z$ scores not shown).

fracture rate. There were two traumatic fractures recorded in the tamoxifen group—a fracture in the right finger and a costal fracture. There was one traumatic fracture in the exemestane group—a fracture of the humerus.

change in BMD status from baseline to month 12. Of patients with a normal BMD value at baseline, a higher proportion of patients treated with exemestane became osteopenic at 12 months compared with those receiving tamoxifen (Table 2). One patient with normal BMD at baseline, who received...
exemestane, became osteoporotic at 12 months. All patients with osteopenia at baseline, who were treated with exemestane, remained osteopenic at 12 months. Of those with osteopenia at baseline and treated with tamoxifen, four patients had normal BMD at 12 months whereas one patient developed osteoporosis at 12 months.

**discussion**

The results of the 12-month analysis in the German bone substudy of the TEAM trial confirm the bone-protective effect of tamoxifen at the spine and the total hip in postmenopausal patients with EBC. However, at the femoral neck, patients on tamoxifen showed a slight increase in BMD at 6 months assessed by DXA, followed by a decrease in BMD at 12 months. Patients receiving exemestane showed a decrease in BMD at the spine and total hip after 6 months; the rate of bone loss stabilised from months 6 to 12. However, patients on exemestane showed a decrease in BMD at the femoral neck after 6 months followed by an increase after 12 months, assessed by DXA.

A possible explanation of the results at the femoral neck is the higher precision error of the measurement at the femoral neck compared with the spine and hip, which has been shown in previous studies [16, 17]. This also corresponds with the larger confidence intervals at the femoral neck at all time points with both treatments. Additionally, our results showed an overlap between the results of both treatment groups after 12 months, leading to a nonsignificant difference between the groups at the femoral neck after 12 months of treatment. This is in contrast to the results at the spine and total hip at all time points.

The impact of BMD changes at different sites on the risk of fracture has been evaluated in a meta-analysis of prospective studies. A decrease of BMD at any site had similar predictive ability for the risk of fracture (relative risk of fracture increased by 1.5-fold for a decrease in BMD of 1 SD). Measurement of BMD at the hip and spine had better predictive ability for fracture risk in the hip and spine, respectively [18].

The results from our substudy are consistent with those reported in a USA substudy of the TEAM trial. There was a more rapid decrease in BMD at the lumbar spine and total hip in patients treated with exemestane initially, followed by a slowing of the rate of bone loss between 12 and 24 months [19].

The IES trial evaluated switching patients to receive exemestane after 2–3 years of tamoxifen compared with continuing tamoxifen [3]. A substudy was conducted to determine the effects on bone health, which showed that patients treated with exemestane experienced rapid bone loss during the first 6 months of treatment at the lumbar spine and hip. Consistent with the results reported here, the rate of bone loss slowed between 6 and 12 and 12 and 24 months [13].

In a further randomised, double-blind study, Lönnig et al. [20] compared the effects of exemestane on bone metabolism.
with placebo. After 2-year treatment, there was no decrease in BMD at the lumbar spine in patients in the exemestane group compared with placebo. However, patients in the exemestane group did experience moderately increased loss of BMD compared with placebo at the femoral neck. Importantly, no patients with normal BMD at baseline developed osteoporosis [20].

Studies with other AIs have also shown AI treatment to be associated with a decrease in BMD. The Anastrozole, Tamoxifen Alone or in Combination (ATAC) study evaluated upfront anastrozole, a nonsteroidal AI, compared with tamoxifen [12]. After 5-year treatment, patients in the anastrozole group experienced a $-6.1\%$ change in BMD from baseline at the lumbar spine and a $-7.2\%$ change in BMD from baseline at the total hip. Patients in the tamoxifen group experienced an increase in BMD from baseline at both the lumbar spine and total hip (2.8\% and 0.7\%, respectively) [12]. Furthermore, in the main ATAC study, there was a statistically significantly increased rate of fractures in patients treated with anastrozole, compared with those treated with tamoxifen (11.0\% versus 7.7\%; respectively; $P < 0.0001$) [21].

In addition, the longer term effects of AIs on bone health were evaluated in the ATAC study. At a median follow-up of 100 months, patients receiving anastrozole had experienced a higher incidence of fractures during active treatment compared with those receiving tamoxifen (annual rate 2.93\% versus 1.90\%, respectively; $P < 0.0001$) [5]. After completion of treatment, there was no difference in the incidence of fractures (annual rate 1.56\% versus 1.51\%, respectively; $P = 0.79$) [5]. In the BIG 1-98 study, after a median follow-up of 51 months, significantly more patients in the letrozole group had experienced fractures compared with those in the tamoxifen group (8.6\% versus 5.8\%, $P < 0.001$) [6]. The IES study has also reported longer term effects on bone health: after a median follow-up of 55.7 months, the fracture rate was 7.0\% with exemestane compared with 4.9\% with tamoxifen ($P = 0.003$) [3].

It has been suggested that nonsteroidal and steroidal AIs may have different effects on BMD. It is possible that the androgenic structure of exemestane may lead to a reduction in adverse events related to bone loss compared with the nonsteroidal AIs [22]. In an animal model, exemestane and its metabolite—17-hydroxyexemestane—were shown to have a protective effect against loss of BMD. In contrast, this protective effect was not seen with the nonsteroidal AI letrozole [23]. The ongoing National Cancer Institute of Canada—Clinical Trials Group (NCIC CTG) MA.27 trial is comparing exemestane with anastrozole for the adjuvant treatment of postmenopausal women with hormone receptor-positive breast cancer. A planned bone substudy of the NCIC CTG MA.27 trial is comparing exemestane with anastrozole for the adjuvant treatment of postmenopausal women with hormone receptor-positive breast cancer. A planned bone substudy of the NCIC CTG MA.27 trial may help determine whether there are any differences between steroidal and nonsteroidal AIs in their effects on BMD.

It is essential that patients and health care professionals are aware of the effective treatment options available to manage the adverse effects of AIs on bone health [24]. Patients at risk of BMD loss during treatment should be identified and managed according to the clinical guidelines [25–28]. It is also important to consider lifestyle, comorbidities and concomitant medications [24] and discuss the importance of compliance with adjuvant therapy before selecting a treatment regimen [11]. Recent guidelines have reviewed clinically relevant risk factors for fracture that can be used to assess overall fracture risk and provide practical guidance for preventing and treating bone loss in women with breast cancer receiving AI therapy [29]. The superior efficacy of adjuvant AI therapy will in most cases outweigh the risk of side effects that can be prevented or easily managed [11, 30].

In conclusion, patients treated with exemestane experience more rapid loss of BMD during the first 6 months of treatment; the rate of bone loss then stabilised after 6–12 months of treatment. There were two fractures in the tamoxifen group and one fracture in the exemestane group. Evaluation of the fracture rate in the overall TEAM trial is necessary to evaluate the effect of exemestane on longer term bone health.

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**disclosures**

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**references**


