Long-term effects of anastrozole on bone mineral density: 7-year results from the ATAC trial


1Academic Unit of Bone Metabolism, University of Sheffield, Sheffield, UK; 2Diagnostic Radiology, Imaging Science and Biomedical Engineering, University of Manchester, Manchester; 3Clinical Development, AstraZeneca, Cheshire; 4The Christie NHS Foundation Trust, University of Manchester, Manchester; 5Cancer Research UK Centre for Epidemiology, Mathematics and Statistics, Queen Mary University of London, Wolfson Institute of Preventive Medicine, London, UK; 6Division of Medical Oncology, Department of Oncology, University of Alberta Cross Cancer Institute, Edmonton, Alberta, Canada; 7Department of Obstetrics and Gynecology, Universität Erlangen-Nürnberg, Erlangen, Germany; 8Cancer Research Centre, Weston Park Hospital, Sheffield, UK

Received 24 March 2010; revised 9 June 2010; accepted 30 July 2010

Background: This ‘Arimidex’, Tamoxifen, Alone or in Combination (ATAC) trial sub-study examined the effects of anastrozole and tamoxifen on bone mineral density (BMD) following 5 years of treatment.

Patients and methods: Lumbar spine and total hip BMD were assessed at years 6 and 7 in a total of 71 eligible patients. In total, 50 patients had evaluable data.

Results: Following anastrozole treatment, the lumbar spine median BMD increased by 2.35% (P = 0.04) and 4.02% (P = 0.0004) at years 6 and 7, while total hip median BMD increased by 0.71% (P = 0.3) and 0.5% (P = 0.8). After tamoxifen treatment, lumbar spine median BMD decreased by 0.73% (P = 0.2) and 0.30% (P = 0.9) at years 6 and 7, while total hip median BMD decreased by 2.09% (P = 0.0003) and 2.52% (P = 0.0002). Patients with a normal BMD or who were osteopenic at 5 years did not become osteoporotic.

Conclusions: Anastrozole treatment-related bone loss did not continue into the off-treatment follow-up period. The recovery in lumbar spine BMD and absence of further loss at the hip is consistent with the reduction in the annual rate of fracture observed after treatment cessation in the main ATAC trial.

Key words: anastrozole, aromatase inhibitors, bone, bone mineral density, breast cancer, tamoxifen

introduction

In postmenopausal women, low estradiol levels are associated with increased bone loss, decreased bone mineral density (BMD) and an increased risk of fracture [1, 2]. As such, cancer treatment-induced bone loss (CTIBL) is an increasing problem for postmenopausal women diagnosed with breast cancer, with spinal and hip fractures resulting in a decreased quality of life [3].

Compared with the selective estrogen receptor modulator, tamoxifen, the third-generation aromatase inhibitors (AIs), such as anastrozole, letrozole and exemestane, have demonstrated superior efficacy and better overall safety in the adjuvant treatment of postmenopausal women with estrogen receptor-positive early breast cancer compared with tamoxifen [4–7]. Although there is general agreement that an AI should be part of adjuvant endocrine therapy, the debate continues over immediate use of an AI versus a sequence/switch strategy [6, 7].

The AIs act by reducing circulating estrogen levels in postmenopausal women. Consequently, one of the major concerns is their effect on bone health and their potential to increase the incidence of cancer treatment-induced osteoporosis and risk of fracture [5, 8–10]. In contrast, tamoxifen has bone-sparing effects, probably related to its partial estrogen agonist activity leading to decreased bone resorption [11].

Due to their potentially deleterious effect on BMD, it is important to understand the effects of long-term AI therapy. Therefore, the ‘Arimidex’, Tamoxifen, Alone or in Combination (ATAC) trial (International Standard Randomised Controlled Trial Number 18233230) included a prospectively designed bone sub-protocol to specifically assess the effects of long-term treatment with anastrozole and tamoxifen on bone. Analyses of these data after a median follow-up of 1, 2 [12] and 5 years [8] showed that anastrozole significantly reduced BMD over the 5-year treatment period compared with tamoxifen.

Here, we present the first assessments of BMD data following completion of 5 years’ initial AI treatment from the ATAC bone sub-study.

patients and methods

study design

The ATAC trial compared the efficacy and tolerability of anastrozole (1 mg/day), alone or in combination with tamoxifen and tamoxifen (20 mg/day)
in postmenopausal women with localised early breast cancer. The combination therapy arm was discontinued following the 33-month median follow-up analysis due to lack of additional benefit over tamoxifen alone. Subsequently, all analyses have focused on the monotherapy arms only [13].

The bone sub-study was a randomised, double-blind, multicentre study carried out within the main ATAC trial. Details on the design and the methodology of this sub-study have been described previously [8, 12]. The sub-study was approved by the relevant ethics committees and international review boards and was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonisation/Good Clinical Practice.

patients

Patients eligible for the off-treatment follow-up were limited to those who participated in the monotherapy arms of the bone sub-protocol who remained recurrence free, were not osteoporotic at 5 years, had evaluable 5-year bone scans for both lumbar and total hip, gave written informed consent to further follow-up and did not possess any of the criteria for withdrawal. Patients with osteoporosis (defined as a T-score less than −2.5 at the lumbar spine or total hip, according to World Health Organization criteria) and those taking bisphosphonates were excluded from this extension study; those with osteopenia (T-score between −1 and −2.5) were included at the investigators’ discretion. In line with the study protocol, no additional drugs or calcium/vitamin D supplements were offered to the patients during the extra 2-year follow-up period.

study assessments

The follow-up assessed the within-group change in BMD (grams per square centimetre) at the lumbar spine and total hip following treatment completion at 5 years as assessed by dual-energy X-ray absorptiometry, using General Electric Lunar Corp (Madison, WI) or Hologic Inc. (Bedford, MA) densitometers. Measurements were made at 6 and 7 years during the 2-year follow-up period after completion of treatment. The 5-year BMD scans were used as a new baseline.

Analysis was carried out locally with quality control checked centrally by Bio-Imaging Technologies Inc. (Newton, PA).

statistical analysis

Lumbar spine and total hip BMD were analysed separately using SAS version 8.2. All analyses and summaries were based on treatment first received. Only data for patients for whom there were evaluable BMD measurements at all time points are presented: for the anastrozole-treated patients, \( n = 21 \) and \( n = 23 \) for the lumbar spine BMD and total hip BMD analysis, respectively. In patients treated with tamoxifen, \( n = 27 \) for both lumbar spine and total hip measurements.

The difference between the 6- and 7-year scans and the 5-year scans was calculated and reported as median percentage change from year 5 with associated interquartile ranges. In addition, these differences were analysed independently using a paired \( t \)-test on the log-transformed BMD values. The results of the statistical analysis were reported as back-transformed geometric means of the ratio of year 5 to year 6 and year 5 to year 7, respectively, with the 95% confidence interval and the \( P \)-value for each.

results

patients

In total, 308 postmenopausal women were recruited to the ATAC bone sub-protocol, and 108 patients in the monotherapy treatment arms completed the bone sub-study (57 patients treated with anastrozole and 51 patients treated with tamoxifen). Eligibility for entry into the extension protocol required documented 5-year scan data and 100 patients had these data (52 anastrozole and 48 tamoxifen). Of these, 4 anastrozole and 1 tamoxifen patients were recorded as osteoporotic at the end of the treatment period and were thus ineligible for entry into the extension protocol [8]. Of the 95 patients who were not osteoporotic and did have recorded scan data at the end of the 5-year study (48 anastrozole and 47 tamoxifen), the total number of osteopenic patients was 62 (35 anastrozole and 27 tamoxifen) and, of these, 25 and 18, respectively, entered the extension sub-study. Of the 33 patients with normal bone scans (13 anastrozole and 20 tamoxifen), 8 and 20, respectively, entered the extension sub-study. There were, therefore, 24 patients with recorded data who did not enter the extension protocol (15 anastrozole and 9 tamoxifen); 10 and 9, respectively, for each treatment group were osteopenic patients, while 5 anastrozole patients and 0 tamoxifen patients had normal BMD measurements [8].

Thus, the bone status of those patients who did not enter the extension study was similar for each treatment group. Overall, 71 patients consented to and were eligible for inclusion in the post-treatment follow-up extension sub-study. A total of 32 patients from the anastrozole group and 38 patients from the tamoxifen group completed the 6-year follow-up visit and 27 and 33 patients completed the 7-year follow-up visit, respectively (Figure 1).

Patient demographics in the 71 patients consenting to the off-treatment follow-up were reasonably well balanced across treatment groups (supplementary online table) and were comparable to the entire population included in the 5-year analysis [8].

changes in BMD following completion of treatment

From years 5–6, lumbar spine BMD increased in 15/23 (65.2%) of patients in the anastrozole group and in 12/27 (44.4%) patients in the tamoxifen group. By year 7, the proportion of patients reporting an increase in lumbar spine BMD had gone up to 20/23 (87.0%) in the anastrozole group and remained at 12/27 (44.4%) in the tamoxifen group.

For total hip BMD, the number of anastrozole-treated patients reporting an increase in BMD was the same at years 6 and 7 (14/21, 66.7%), whereas only 4/27 (14.8%) and 6/27 (22.2%) tamoxifen-treated patients reported an increase in total hip BMD at years 6 and 7, respectively.

Compared with the 5-year values, median lumbar spine BMD increased by +2.35% at year 6 (interquartile range = −5.34 to 8.19, \( P = 0.04 \)) and +4.02% at year 7 (interquartile range = −6.04 to 14.01, \( P = 0.0004 \)) in anastrozole-treated women. In the tamoxifen-treated group, there was a decrease in BMD of −0.79% at year 6 (interquartile range = −10.61 to 4.35, \( P = 0.2 \)) and −0.3% at year 7 (interquartile range = −7.43 to 10.22, \( P = 0.9 \)) (Figure 2A).

Median total hip BMD for anastrozole-treated women stabilised during the off-treatment follow-up period with +0.71% at year 6 (interquartile range = −9.42 to 4.63, \( P = 0.3 \)) and +0.5% at year 7 (interquartile range = −8.74 to 4.27, \( P = 0.8 \)) compared with year 5. In the tamoxifen group, median BMD
had decreased by $-2.09\%$ at year 6 (interquartile range $-4.34$ to $5.70$, $P = 0.0003$) and $-2.52\%$ at year 7 (interquartile range $-9.5$ to $8.02$, $P = 0.0002$) (Figure 2B).

There was a statistically significant increase within the anastrozole 1 mg treatment group at years 6 and 7 compared with year 5 (Table 1), while the small decreases in lumbar spine BMD within the tamoxifen 20 mg treatment group at years 6 and 7 were not statistically significant (Table 1).

Similarly, the change in total hip BMD at years 6 and 7 compared with year 5 showed a slight, but statistically significant, loss within the tamoxifen 20 mg treatment group (Table 1), while there was a small increase in total hip BMD within the anastrozole 1 mg treatment group at year 6 (and a marginal decrease at year 7) that were not statistically significant (Table 1).

Geometric mean BMD values for lumbar spine and total hip from the start of treatment (year 0) are illustrated in Figure 2C and D, respectively. These show a return of bone after the 5-year treatment period but not to the baseline levels.

In this extension study, no woman who had a normal BMD or who was osteopenic at year 5 became osteoporotic at years 6 or 7, in either treatment group (Table 2). Some patients who were osteopenic at treatment completion (anastrozole $n = 9$; tamoxifen group $n = 4$) did not have a bone scan recorded at year 7 (Table 2). Although the reason for this is unclear, a likely explanation is that these patients dropped out of the study after 5 years to receive bisphosphonate treatment.

**Discussion**

The primary objective of this follow-up analysis of the ATAC bone sub-study was to provide important additional information on the skeletal health effects of anastrozole after cessation of treatment.

In patients entering the follow-up extension of the bone sub-protocol, analysis of the two treatment groups at year 7 demonstrated that the greater bone loss seen with anastrozole over tamoxifen during the 5-year active treatment period did not continue into the off-treatment follow-up, and there was evidence of partial recovery in BMD at the lumbar spine and no further loss in BMD at the hip in the anastrozole group.

Caution must be taken, however, concerning the generalisability of these findings, due to the low number of patients completing the 7-year follow-up period.

In the sub-set of patients completing the off-treatment follow-up with normal BMD at 5 years, or identified as osteopenic at 5 years, none became osteoporotic after adjuvant treatment. The recently published results of the main ATAC study [14] showed similar fracture rates in the anastrozole- and tamoxifen-treated patients during the off-treatment period. These findings are consistent with the recovery in BMD confirmed after treatment completion.

Several trials have indicated that other AIs (letrozole and exemestane) can be associated with an increased risk of fractures [15–18] and increased rates of bone loss during the
treatment phase [16, 17, 19]. Similarly, the ATAC bone sub-protocol study showed anastrozole-related BMD loss during the treatment phase [8] with a concomitant increased rate of fractures [14], both of which subsequently recovered following cessation of treatment.

The ATAC bone sub-study is the first to present long-term follow-up data on BMD beyond 5 years of adjuvant AI therapy. Current treatment guidelines recommend the inclusion of an AI for optimal adjuvant endocrine therapy [20–22]. Bisphosphonates have been shown to prevent and treat osteoporosis in postmenopausal women and to reduce CTIBL. However, it has been reported that their use in the context of adjuvant AI therapy need only be initiated when the risk of fragility fractures is high, such as a previous diagnosis of osteoporosis, age >75 years and additional risk factors for fracture, BMD T-score less than −2.0, or an on-treatment fragility fracture has occurred [4, 23, 24].

Despite the relatively low number of evaluable patients, this ATAC bone sub-study reinforces the suggestion that, for patients in whom pre-existing osteopenia is excluded at the start of treatment, or where osteopenia is identified at the end of long-term anastrozole treatment, further monitoring or preventative bone-loss strategies are no longer necessary beyond those normally used for all postmenopausal women [8].

The latest results from the main ATAC trial and bone sub-protocol show that, on completion of anastrozole treatment, fragility fracture rates decrease back to levels similar to those observed with tamoxifen, and fractures occurring after treatment completion are not associated with patients becoming osteoporotic after AI treatment.

Overall, the prevention of CTIBL in long-term adjuvant AI breast cancer therapy remains a high priority [25]. What these study results demonstrate is that, in contrast to the beneficial effects of anastrozole on breast cancer recurrence which extend

---

**Figure 2.** Median percent change (±interquartile ranges) in bone mineral density (BMD) for (A) lumbar spine and (B) total hip, for the off-treatment follow-up period (years 6 and 7) compared with year 5; mean BMD for (C) lumbar spine and (D) total hip, for the 5-year adjuvant treatment (years 1–5) and off-treatment (years 6 and 7) periods compared with the start of treatment (year 0).

*Year 6 vs Year 5, P = 0.0003; **Year 7 vs Year 5, P = 0.0002
Analysis was for patients on whom there was data at each timepoint.

Time 0 years plots the baseline BMD data for those patients who subsequently entered the extension protocol. Data at Years 5, 6 and 7 are based on the patients within this group with available data for each time point at years 5, 6 and 7.
substantially beyond the cessation of treatment [14], anastrozole-associated BMD loss begins to resolve immediately after treatment cessation and any bone loss associated with anastrozole can be monitored and managed as needed [25–29].

In conclusion, this study is the first to quantify the long-term impact on BMD of AI treatment in women with early breast cancer. Anastrozole-related bone loss appears to be manageable and, therefore, any risk to bone health should be weighed against its overall efficacy and tolerability profile for the treatment of hormone-sensitive early-stage postmenopausal breast cancer.

funding
AstraZeneca, who provided support for the conduct of the study, data collection and project management, to RE; AstraZeneca and Aventis to JC.

acknowledgements
We gratefully acknowledge the participating patients and study investigators for their invaluable contribution. We thank Varinia Muñoz, PhD, of Complete Medical Communications, who provided medical writing support funded by AstraZeneca.

disclosure
RE has acted as a consultant for and received research funding from AstraZeneca. GC is an AstraZeneca employee and holds shares in the company. AH is a member of the Speaker’s Bureau at AstraZeneca. JC is a statistical consultant for AstraZeneca and has received research funding from AstraZeneca and Aventis. JA, JM, MWB and REC have no conflicts of interest to declare.

references

Table 1. Primary analysis of change in lumbar spine and total hip BMD from 5 to 6 and from 5 to 7 years (primary analysis population with data at 5, 6 and 7 years)

<table>
<thead>
<tr>
<th>Within treatment comparisons</th>
<th>Year 7 or 6</th>
<th>Year 5</th>
<th>Year 7 or 6 versus year 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>n gmean (g/cm²)</td>
<td>n gmean (g/cm²)</td>
<td>Ratio of gmean(s)</td>
<td>Two-sided 95% CI</td>
</tr>
<tr>
<td>Lumbar spine* 5–6 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anastrozole 1 mg</td>
<td>23</td>
<td>1.042</td>
<td>23</td>
</tr>
<tr>
<td>Tamoxifen 20 mg</td>
<td>27</td>
<td>1.044</td>
<td>27</td>
</tr>
<tr>
<td>5–7 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anastrozole 1 mg</td>
<td>23</td>
<td>1.064</td>
<td>23</td>
</tr>
<tr>
<td>Tamoxifen 20 mg</td>
<td>27</td>
<td>1.054</td>
<td>27</td>
</tr>
<tr>
<td>Total hip* 5–6 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anastrozole 1 mg</td>
<td>21</td>
<td>0.912</td>
<td>21</td>
</tr>
<tr>
<td>Tamoxifen 20 mg</td>
<td>27</td>
<td>0.934</td>
<td>27</td>
</tr>
<tr>
<td>5–7 years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anastrozole 1 mg</td>
<td>21</td>
<td>0.907</td>
<td>21</td>
</tr>
<tr>
<td>Tamoxifen 20 mg</td>
<td>27</td>
<td>0.927</td>
<td>27</td>
</tr>
</tbody>
</table>

aData presented for patients who had evaluable BMD measurements at all visits.
BMD, bone mineral density; CI, confidence interval; gmean, geometric mean; n, number of patients.

Table 2. T-scores shift table for lumbar spine and total hip for the overall off-treatment follow-up period (years 5–7, primary analysis population)

<table>
<thead>
<tr>
<th>Status at treatment completion</th>
<th>Shift to Anastrozole 1 mg (N = 33)</th>
<th>Shift to Tamoxifen 20 mg (N = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal bone 8 14</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteopenic 0 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoporotic 0 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not recorded* 0 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteopenic 2 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal bone 14 11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Osteoporotic 0 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not recorded* 9 4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Osteoporosis and osteopenia were defined as a T-score less than −2.5 or a T-score between −1 and −2.5 at the lumbar spine or total hip, respectively. T-score is the minimum of the mean lumbar spine and mean total hip T-scores. If either of the BMD measurements was missing, the classification was done on the basis of the single measurement. No patient was osteoporotic at entry into the extension study.

*No total hip and lumbar spine bone mineral density measurements due to missing dual-energy X-ray absorptiometry scan or patient discontinued.


