



HAL
open science

A study of the effects of the aromatase inhibitors anastrozole and letrozole on bone metabolism in postmenopausal women with estrogen receptor-positive breast cancer

Fiona M. Mccaig, Lorna Renshaw, Linda Williams, Oliver Young, Juliette Murray, Elizabeth J. Macaskill, Mary Mchugh, Rosemary Hannon, J. Michael Dixon

► **To cite this version:**

Fiona M. Mccaig, Lorna Renshaw, Linda Williams, Oliver Young, Juliette Murray, et al.. A study of the effects of the aromatase inhibitors anastrozole and letrozole on bone metabolism in postmenopausal women with estrogen receptor-positive breast cancer. *Breast Cancer Research and Treatment*, 2009, 119 (3), pp.643-651. 10.1007/s10549-009-0646-0 . hal-00535417

HAL Id: hal-00535417

<https://hal.science/hal-00535417>

Submitted on 11 Nov 2010

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

A study of the effects of the aromatase inhibitors anastrozole and letrozole on bone metabolism in postmenopausal women with estrogen receptor-positive breast cancer

Fiona M. McCaig · Lorna Renshaw · Linda Williams · Oliver Young · Juliette Murray · Elizabeth J. Macaskill · Mary McHugh · Rosemary Hannon · J. Michael Dixon

Received: 17 August 2009 / Accepted: 10 November 2009 / Published online: 26 November 2009
© Springer Science+Business Media, LLC. 2009

Abstract ALIQUOT (Anastrozole vs. Letrozole, an Investigation of Quality Of Life and Tolerability) was a prospective, open-label, randomized pharmacodynamic study designed to assess the effects of aromatase inhibitors (AIs) on bone turnover in healthy postmenopausal women with estrogen receptor-positive breast cancer. Ninety-four patients were randomized to receive either 12 weeks of letrozole (2.5 mg; $n = 42$) followed by 12 weeks of anastrozole (1 mg), or 12 weeks of anastrozole (1 mg; $n = 42$) followed by 12 weeks of letrozole (2.5 mg). After completion of the study period, patients in the immediate adjuvant group were either switched to tamoxifen ($n = 38$) or continued on anastrozole or letrozole. In the beginning of the study, 42 patients had taken tamoxifen within 3 months. Patients taking drugs likely to affect bone metabolism, including bisphosphonates, were excluded. Eighty-four patients had complete sample measurements

and were included in the analysis. Prior tamoxifen therapy resulted in a significantly lower mean baseline procollagen type 1 N-terminal propeptide (PINP) compared with patients with no prior tamoxifen. There were no significant differences in bone markers between AIs at any time. By 6 months, significant increases were seen in PINP, C-terminal telopeptides (CTX), bone specific alkaline phosphatase (ALP), and urinary N-terminal telopeptides (NTX). Patients with prior tamoxifen had significantly greater increases than patients with no prior tamoxifen. Patients treated with 3 months of tamoxifen following 6 months of an AI showed a significant decrease in markers of bone resorption, serum CTX and urinary NTX. In conclusion, AI-induced bone turnover increases over time. Anastrozole and letrozole produce similar effects on bone metabolism and turnover. Stopping tamoxifen therapy and starting AIs results in a significantly greater increase in bone turnover compared with commencing AIs in tamoxifen-naïve patients. Patients given tamoxifen following AI therapy showed a decrease in markers of bone resorption.

Where/when study was presented in part elsewhere: San Antonio Breast Cancer Symposium, December 13–16, 2007, San Antonio, TX, in poster format; the European Breast Cancer Conference, April 15–19, 2008, Berlin, as an oral presentation; the Association of Surgeons of Great Britain and Ireland Surgical Meeting (ASGBI), May 14–16, 2008, Bournemouth, UK, as an oral presentation.

Keywords ALIQUOT · Anastrozole · Bone markers · Breast cancer · Letrozole

F. M. McCaig · L. Renshaw · O. Young · J. Murray · E. J. Macaskill · M. McHugh · J. M. Dixon (✉)
Breakthrough Research Unit, Edinburgh Breast Unit, Western General Hospital, Edinburgh EH4 2XU, Scotland, UK
e-mail: jmd@ed.ac.uk

L. Williams
Centre for Population Health Sciences, Medical School,
University of Edinburgh, Edinburgh, Scotland, UK

R. Hannon
Unit of Bone Metabolism, Metabolic Bone Centre,
Northern General Hospital, Sheffield, England, UK

Introduction

Third-generation aromatase inhibitors (AIs) are active treatments in postmenopausal women with estrogen receptor-positive (ER+) breast cancer and are increasingly used. In the neoadjuvant setting, they have definitive advantages over tamoxifen, once the mainstay endocrine therapy for postmenopausal women with hormone-sensitive breast cancer. Data indicate that the AIs are also superior to tamoxifen, in terms of disease-free survival

(DFS), in the adjuvant setting [1, 2]. Tamoxifen is an antiestrogen that binds to the ER in place of estrogen and thereby blocks estrogen-mediated signaling [3]. Tamoxifen has partial agonist activity and stimulates ER activity in some organs such as bone, resulting in bone-sparing effects; however, in the endometrium, its partial estrogenic agonist activity results in an increased risk of endometrial cancer [4–6].

Concern over the long-term effects of adjuvant AI therapy on bone health has also surfaced, as studies have shown a higher fracture rate for AIs compared with tamoxifen [1, 2, 7, 8]. AIs prevent estrogen biosynthesis in peripheral tissues by inhibiting aromatase, the cytochrome P450 enzyme that catalyses the conversion of adrenal androgens (androstenedione and testosterone) to estrogens (estrone and estradiol). There are two types of AIs, the nonsteroidal, competitive inhibitors anastrozole and letrozole and the steroidal, non-competitive inhibitor exemestane. Each substantially reduces circulating estrogen, which increases bone turnover and results in bone mineral loss. Letrozole decreases circulating estrogen levels to a greater degree than anastrozole [9]. This in turn could lead to a greater degree of osteoporosis and an increased rate of fractures. There is clear evidence that bone turnover markers are strong predictors of future fractures [10]. The aim of this study was to determine whether there is a significant difference between letrozole and anastrozole in their effects on bone turnover in a series of postmenopausal women with ER+ operable breast cancers.

Patients and methods

Study design

ALIQUOT (Anastrozole vs. Letrozole, an Investigation of Quality Of Life and Tolerability) was a prospective, open-label, randomized pharmacodynamic study. Bone turnover markers were measured in a subset of 94 out of 185 postmenopausal women with invasive ER+ breast cancer. Patients were randomized as part of their adjuvant endocrine therapy to receive either 12 weeks of letrozole followed by 12 weeks of anastrozole or 12 weeks of anastrozole followed by 12 weeks of letrozole. The study was approved by the Lothian Research Ethics Committee and carried out in accordance with the Declaration of Helsinki and in keeping with Good Clinical Practice. All patients were treated in the Edinburgh Breast Unit. Following informed consent, each patient was randomized to receive 3 months of anastrozole (1 mg) or letrozole (2.5 mg) orally once daily in a crossover study (Fig. 1). Some patients received adjuvant AI therapy immediately following surgery, while other patients had already

received adjuvant tamoxifen and then received AIs in the extended adjuvant setting. Each drug was administered for 12 weeks, and after completion of the study period, patients in the immediate adjuvant group were either switched to tamoxifen or continued on anastrozole or letrozole. All those having extended adjuvant therapy continued on letrozole unless they expressed a specific preference for anastrozole, as letrozole is approved for extended therapy. The study ran between January 2004 and December 2006.

Patients

All patients included had histologically confirmed invasive cancer that was ER+ (ALLRED score ≥ 4). Postmenopausal status was defined as amenorrhea for 1 year and/or luteinizing hormone with follicular stimulating hormone levels in the postmenopausal range. Postmenopausal women who had early invasive breast cancer (T1-3, N0-1, M0) and who were able to give informed consent were considered eligible. Of note, the only post chemotherapy patients were those who had completed 5 years of tamoxifen. All premenopausal women; women receiving concurrent or previous chemotherapy (within the last 4 years); women taking concomitant hormonal therapy, including hormone replacement therapy; women taking drugs likely to affect bone metabolism, including steroids and bisphosphonates; and patients unable to give informed consent were excluded from entry into the study.

Ninety-four postmenopausal women with ER+ breast cancer who were suitable for adjuvant or extended adjuvant treatment with an AI and were on no drugs likely to have an effect on bone metabolism were enrolled (Fig. 2). Patients were either due to start endocrine therapy as their first treatment after surgery and were therefore tamoxifen-naïve ($n = 52$) or were finishing 5 years of tamoxifen and beginning extended adjuvant therapy ($n = 42$). Each patient was randomized (1:1) to receive 6 months of AI therapy, which included 3 months of anastrozole followed by 3 months of letrozole or 3 months of letrozole followed by 3 months of anastrozole (Fig. 1). Patients with no prior exposure to tamoxifen were thereafter started on 20 mg of tamoxifen daily for 3 months.

Eighty-four patients had complete sample measurements and were included in the analysis. Ten patients were excluded from analysis because of technical problems with the samples. One patient was later removed from the analysis, as she was found to be taking medication likely to affect bone turnover; this patient did not exhibit an unusual response to therapy.

The median age of the patients was 63 years (range, 40–87). The median age was 61 and 65 years in the post-tamoxifen and no-prior-tamoxifen groups, respectively.

Fig. 1 Anastrozole versus Letrozole, an Investigation of Quality Of Life and Tolerability (ALIQOT) open-label crossover study design. In this analysis, postmenopausal women with hormone receptor-positive breast cancer received either 3 months of anastrozole followed by 3 months of letrozole ($n = 42$) or the opposite sequence ($n = 42$). *ER+* estrogen receptor-positive

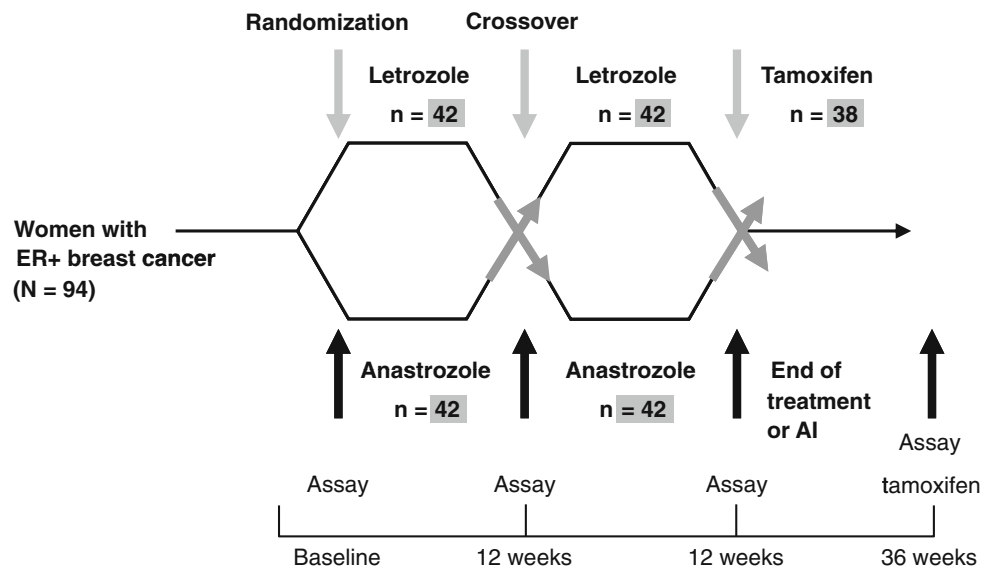
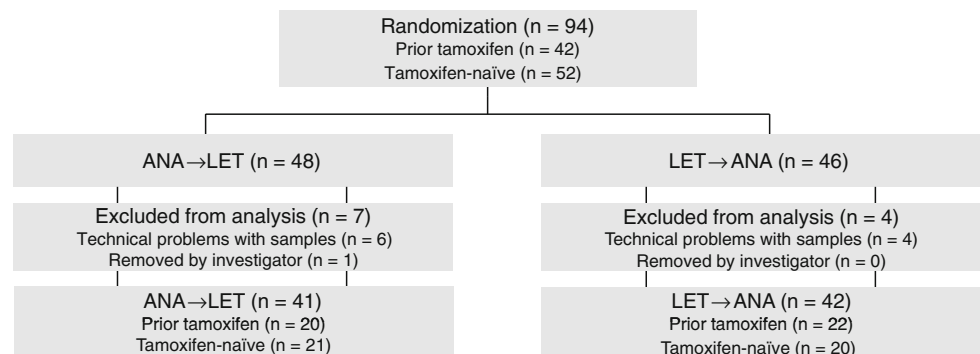


Fig. 2 ALIQOT CONSORT diagram



Further patient demographics are shown in Table 1. Forty-six patients were initially randomized to letrozole first followed by anastrozole, and 48 were initially randomized anastrozole followed by letrozole.

Blood samples and bone marker measurements

Ninety-four patients (52 after surgery and 42 after tamoxifen) had fasting blood and urine collected before and after 12 weeks of each drug. Of the aforementioned 52 patients, 38 had fasting samples collected 12 weeks after completing AIs and commencing tamoxifen (Fig. 1). Blood and urine samples for bone marker measurements were

collected following an overnight fast, at the same time of day and on the same day of the week at the beginning and end of each 12-week period of drug treatment. The timing of samples was scheduled to minimize diurnal and diet-related effects. Plasma samples were separated by centrifugation and stored at -80°C until analyzed. The second voided urine of the day was collected for measurement of urinary bone markers. Urine samples were also stored at -80°C .

The crosslinked N and C telopeptides of type I collagen, urinary N-terminal telopeptides (uNTX) and serum C-terminal telopeptides (sCTX), were measured as markers of bone resorption, and procollagen type I N-terminal

Table 1 Patient demographics

	Post 5 years of tamoxifen ($n = 42$)	No prior tamoxifen ($n = 52$)
Median age at entry, years (range)	61 (40–78)	65 (44–87)
Mean baseline height, cm (SE)	161.7 (1.21)	161.9 (0.88)
Mean baseline weight, kg (SE)	72.0 (2.13)	74.9 (2.24)
Prior hormone replacement therapy (n)	17	20
Hysterectomy (n)	11	5
Bilateral oophorectomy (n)	3	0

propeptide (PINP) and bone-specific alkaline phosphatase (bone ALP) were measured as markers of bone formation.

Urinary NTX was measured by an automated Vitros Eci chemiluminescence immunoassay (Ortho Clinical Diagnostics) and was expressed as a ratio to urinary creatinine, which was measured by a dry slide method (Vitros 250, Ortho Clinical Diagnostics). Interassay coefficient of variations (CV) was 6.2%, and the intra-assay CV was not calculated, as NTX was run on an autoanalyser. Serum CTX was measured by an enzyme-linked immunoassay (Crosslaps[®], Nordic Bioscience Diagnostics A/S). Intra-assay CV was 3.2%, and interassay CV was 3.0%.

Intact PINP was measured by radioimmunoassay (Orion Diagnostics Oy). The interassay CV was 5.7%, and the intra-assay CV was 5.2%. Bone ALP was measured by the Ostase[®] assay, a paramagnetic chemiluminescent method, on an Access[®] autoanalyser (Beckman Coulter Inc). The interassay CV was 2.3%, and the intra-assay CV was not calculated, as bone ALP was run on an autoanalyser.

Serum parathyroid hormone (PTH) was measured by enzyme-linked immunoassay (BiomericaInc). The interassay CV was 7.2%, and the intra-assay CV was 3.7%.

Increases in NTX and CTX indicate bone resorption, while increases in PINP and bone-specific ALP indicate bone formation. These markers, together PTH, were measured at the Academic Unit of Bone Metabolism, Sheffield, UK.

Statistical analysis

In order to have sufficient data to detect statistically significant differences in bone turnover, it was estimated that 20% of patients on each AI would need to have significant changes in bone turnover. For this proportion to be able to exclude 10%, 86 patients would be required over the two groups. To take this into account, the possibility of loss to follow-up, or failure to comply, the sample size was increased by 10% to 94.

The statistical analysis was conducted by an independent statistician. Hormone therapy for each patient was coded to maintain the blind assessment and avoid bias. Analysis of the variables was conducted using mixed models and repeated measures, since measurements were of the same patient over a series of time points. Whether the patients had also taken tamoxifen for 5 years was also included in the model. Bone ALP and PTH were log transformed to achieve normality prior to analysis.

Ten patients were unable to be included in the analysis because of technical problems arising with the samples. An additional patient was removed from the analysis, because she was found to be taking medication likely to affect bone turnover.

Results

Patients

Ninety-four postmenopausal women with ER+ breast cancer were enrolled in this study. Baseline patient characteristics are shown in Table 1. Overall, patient demographics were similar between the two groups. The median age of patients who had completed 5 years of tamoxifen was 61, and the median age of those who had received no prior tamoxifen was 65. More patients who had received 5 years of tamoxifen had undergone hysterectomy and bilateral oophorectomy compared with those who had not received tamoxifen.

Effect of treatment on bone turnover

Effect of prior tamoxifen

There were significant differences from baseline between the tamoxifen-naïve group and patients who had received prior tamoxifen for PINP levels (47.9 vs. 37.3; $P = 0.005$) and sCTX levels (0.67 vs. 0.49; $P = 0.0003$) (Table 2). Figure 3 shows that patients who received prior tamoxifen had a significantly greater increase in levels of PINP (Fig. 3a), sCTX (Fig. 3b), uNTX (Fig. 3c), and ALP (Fig. 3d) at 3 and 6 months than did tamoxifen naïve patients. Results are presented as percentage change from baseline for each group. PTH (Fig. 3e) is an indirect measure of overall bone turnover, and greater reductions between the two groups also reflect the increased bone turnover in patients previously treated with tamoxifen.

Differences between letrozole and anastrozole

Both AIs had major effects on all bone markers, although there were no significant differences between the drugs at the 3- or 6-month time points for any of the parameters measured (all $P > 0.10$). This was independent of the drug sequencing. Changes from the baseline are shown in Table 2 and Fig. 4. Both letrozole and anastrozole markedly increased bone turnover.

Changes over time

There were significant increases in both bone resorption and bone formation between 0 and 3 months and 3 and 6 months for PINP, sCTX, bone ALP (all $P < 0.0001$), and uNTX ($P = 0.04$). PTH showed no change. The group that had previously received tamoxifen had significantly greater increases (all $P < 0.0006$) in markers of bone resorption together with significantly larger rises in markers of bone

Table 2 Percentage change from baseline

		Percentage change from baseline			
		Study drug		Tamoxifen for 5 years	
		Anastrozole	Letrozole	No ($n = 41^a$)	Yes ($n = 42$)
PINP	Baseline	42.74		47.9	37.3
	3 months	+16.3%	+16.8%	+7.5%	+25.7%
	6 months	+46.4%	+32.7%	+23.2%	+55.8%
sCTX	Baseline	0.59		0.67	0.49
	3 months	+30.3%	+26.2%	+14.6%	+41.9%
	6 months	+44.8%	+43.2%	+26.2%	+61.8%
uNTX	Baseline	44.59		48.7	40.5
	3 months	+29.0%	+26.2%	+17.9%	+37.4%
	6 months	+48.1%	+40.7%	+26.1%	+62.7%
ALP ^{Log transformed}	Baseline	2.52		2.54	2.50
	3 months	+2.3%	+1.6%	+0.4%	+3.5%
	6 months	+6.6%	+5.4%	+4.8%	+7.2%
PTH ^{Log transformed}	Baseline	4.06		4.07	4.06
	3 months	-1.1%	-2.7%	-1.5%	-2.3%
	6 months	-3.0%	-2.4%	-0.4%	-5.0%

^a 11 patients removed at analysis stage

PINP procollagen type I N terminal propeptide, sCTX serum C-terminal telopeptides, uNTX urinary N-terminal telopeptides, ALP alkaline phosphatase, PTH parathyroid hormone

formation at all time points compared with the tamoxifen-naïve group. The differences for PTH were also significant, with smaller rises in the prior tamoxifen group ($P = 0.0004$).

Effects of AIs followed by tamoxifen

There were significant differences between the drugs (anastrozole vs. letrozole vs. tamoxifen-following AI) for the markers of bone resorption, sCTX ($P = 0.0004$), and uNTX ($P = 0.0009$), as shown in Table 3. In both cases, anastrozole and letrozole were significantly different from tamoxifen, but not from each other. However, only a limited number of patients had data for this analysis, so some degree of care must be taken in the interpretation of the results. There was no influence on mean percentage change following tamoxifen by the sequence of the previous AIs (all $P > 0.5$).

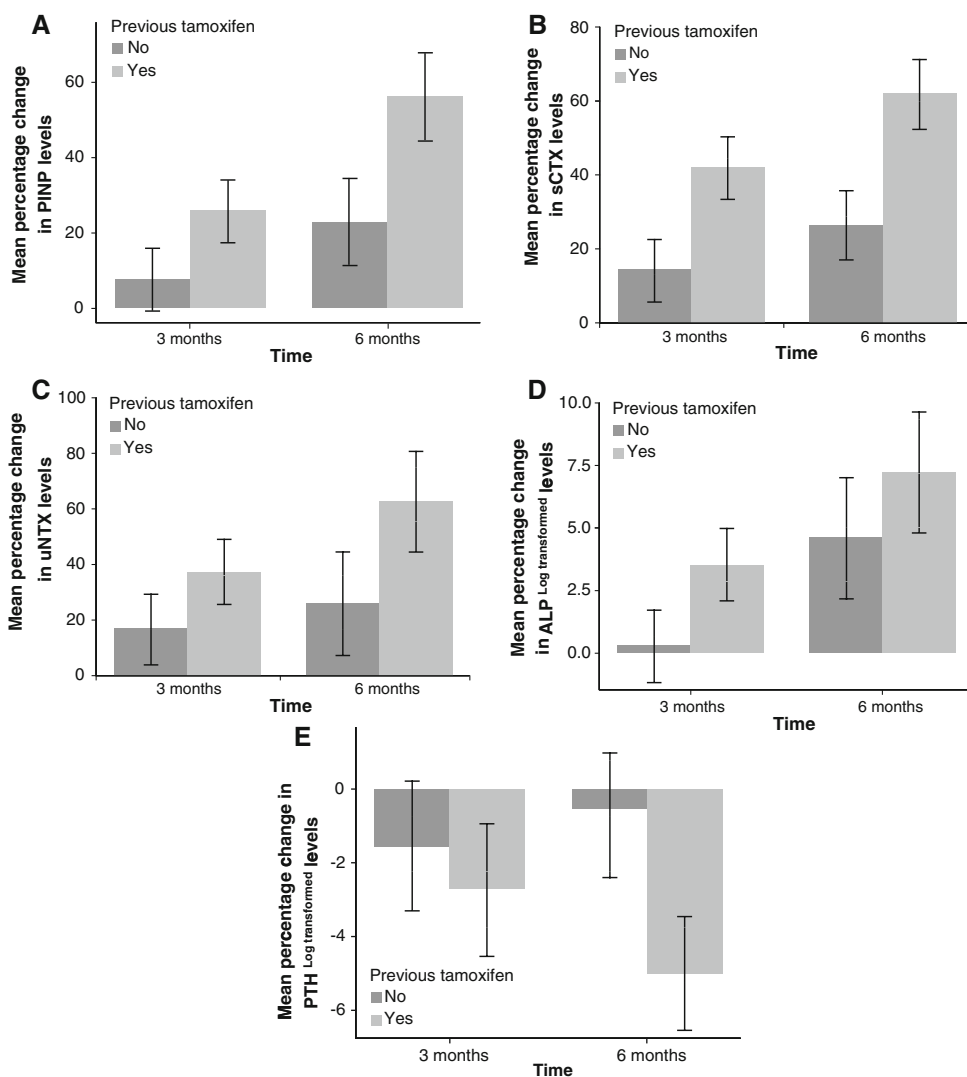
Discussion

Anastrozole and letrozole are potent third-generation AIs that cause profound suppression of plasma estrogen levels in postmenopausal women [11, 12]. There is evidence that letrozole is a more potent inhibitor of aromatase, and that at clinically used doses, letrozole reduces estrogen levels to a

greater degree than anastrozole [9, 13]. This study showed that 6 months of treatment with letrozole and anastrozole induces a significant increase in bone turnover, and that this is further augmented in patients who have already received 5 years of adjuvant tamoxifen therapy. Despite the greater ability of letrozole (2.5 mg) to lower circulating estrogen levels compared with anastrozole (1 mg) [9], the effects on bone metabolism are similar at clinically used doses. These effects increase with time, and greater bone turnover is evident at 6 months compared with 3 months, although there is no difference between the drugs. There is therefore unlikely to be any difference between these drugs in fracture rate or the rate of osteoporosis. In postmenopausal women, AI therapy has been associated with increases in bone turnover and bone loss at an average rate of 1 to 3% per year [14]. Consequently, an increase in fracture incidence is also observed when compared with that seen during tamoxifen use [14]. In the Anastrozole, Tamoxifen, Alone or in Combination (ATAC) trial, the fracture rate for anastrozole was 11% at a median follow-up of 68 months, versus 7.7% for tamoxifen [1]. Similarly, in the subset analysis restricted to the monotherapy arms of the Breast International Group (BIG) 1-98 trial, the fracture rate for letrozole was 8.6% at a median follow-up of 51 months, compared with 5.8% for tamoxifen [15].

Recent trials indicate that a 5-year course of tamoxifen is no longer the optimum therapy for postmenopausal

Fig. 3 Levels of bone markers at 3 and 6 months in tamoxifen-naïve group versus tamoxifen-treated group: procollagen type I N terminal propeptide (PINP) (a), serum C-terminal telopeptides (sCTX) (b), urinary N-terminal telopeptides (uNTX) (c), alkaline phosphatase (ALP) (d) and parathyroid hormone (PTH) (e). Error bars: 95% confidence interval



women with early ER+ breast cancer. The ATAC trial and the Intergroup Exemestane Study (IES) showed that initial treatment with an AI or switching to an AI was better, in terms of risk reduction, than tamoxifen. Estradiol levels have been reported to be virtually undetectable in patients taking AIs, and this partly explains the high rate of bone loss and greater risk of fractures. Deterioration in bone health is a major concern for patients taking AIs long-term. In our study, there was no difference between letrozole and anastrozole with regard to their effects on bone metabolism. Our findings are similar to those in the Letrozole, Exemestane and Anastrozole in healthy Postmenopausal women (LEAP) study, which also reported that the third-generation AIs, whether steroidal or nonsteroidal, are similar with respect to their effects on bone [7].

Postmenopausal women with hormone-sensitive breast cancer receiving adjuvant AI therapy are at risk for AI-associated bone loss, but it is important to note that this bone loss is manageable, and AI therapy should not be

withheld for fear of bone loss. The American Society of Clinical Oncology recommends bone mineral density (BMD) assessments in all women beginning adjuvant AI therapy. While most women will have normal BMD, routine screening may identify women who are at increased risk for bone loss and are candidates for bisphosphonate therapy [16]. Randomized clinical trials such as the Zometa-Femara Adjuvant Synergy Trial (Z-FAST in the United States and ZO-FAST in Europe) support the use of zoledronic acid (4 mg), a bisphosphonate, every 6 months to prevent AI-associated bone loss [17, 18]. In addition to calcium and vitamin D supplementation, any patient who is starting AI therapy and has a T -score < -2.0 should receive zoledronic acid (4 mg) twice yearly [19]. Zoledronic acid is also being recommended for any patient who is receiving AI therapy and has any two of the following risk factors: T -score < -1.5 , age > 65 years, family history of hip fracture, personal history of fragility fracture after age 50, or oral corticosteroid use > 6 months [19].

Fig. 4 Differences in bone markers at 3 and 6 months between letrozole and anastrozole: procollagen type I N terminal propeptide (PINP) (a), serum C-terminal telopeptides (sCTX) (b), urinary N-terminal telopeptides (uNTX) (c), alkaline phosphatase (ALP) (d) and parathyroid hormone (PTH) (e). Error bars: 95% confidence interval

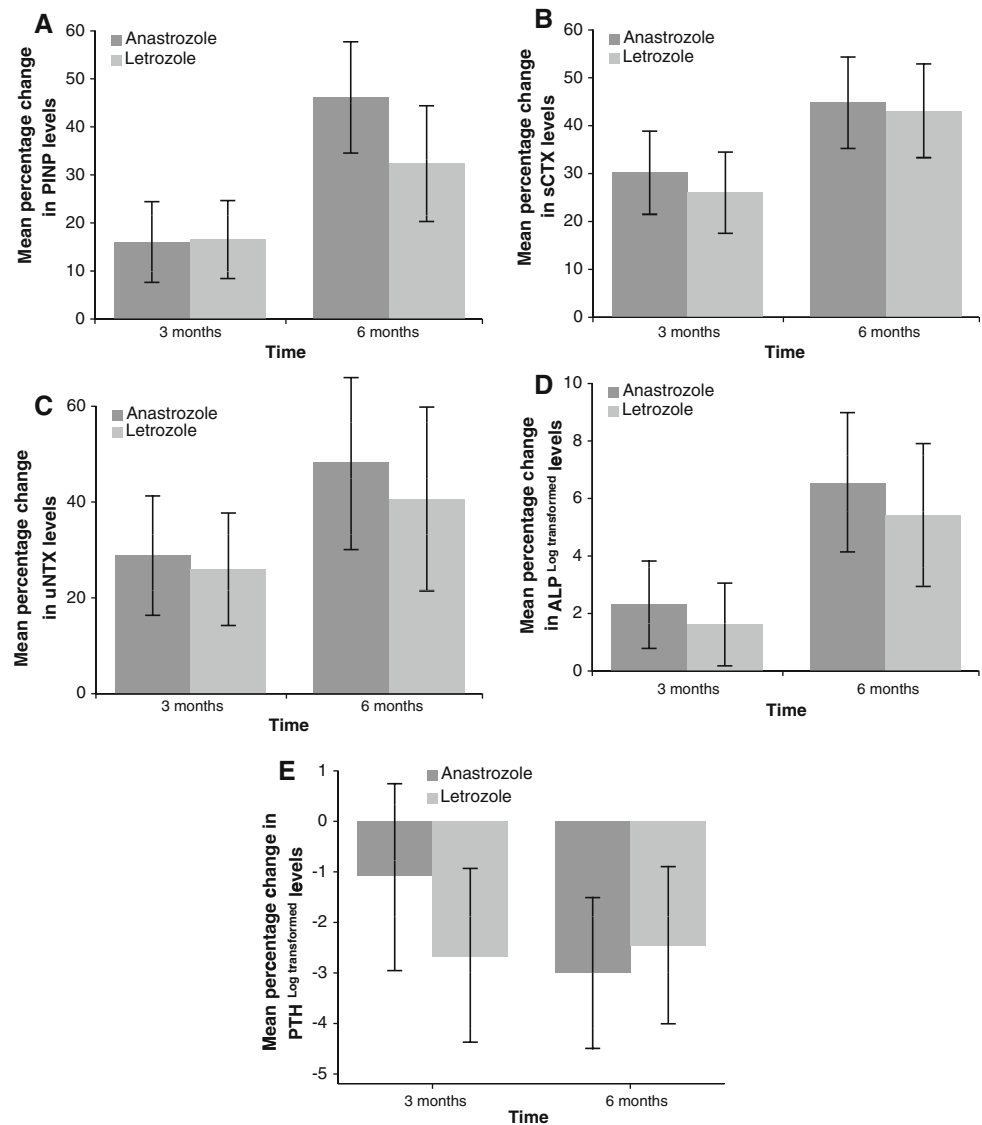


Table 3 Comparison of Anastrozole, Letrozole and Tamoxifen-following aromatase inhibitor

	Drug (mean percentage change, 95% CI)			P value
	Anastrozole	Letrozole	Tamoxifen (following 6 months of AI)	
PINP ($n = 31$)	11.12 (−9.20 to 31.43)	8.98 (−11.94 to 29.90)	−4.18 (−20.30 to 11.93)	0.51
sCTX ($n = 38$)	−6.39 (−13.00 to 0.22)	−7.56 (−14.05 to −1.08)	−20.00 (−26.03 to −13.97)	0.0004
uNTX ($n = 30$)	9.96 (−1.31 to 21.23)	7.61 (−3.44 to 18.66)	−10.20 (−21.69 to 0.87)	0.0009
ALP ($n = 31$) (transformed)	0.79 (−0.88 to 2.45)	0.71 (−1.08 to 2.50)	−0.03 (−2.93 to 2.87)	0.82

N's represent numbers patients who had data for all three drugs. Total number of tests performed for anastrozole, letrozole and tamoxifen, respectively, was: PINP: 76, 76, 31; sCTX: 76, 76, 38; uNTX: 76, 76, 30 and ALP: 76, 76, 31

AI aromatase inhibitor, CI confidence interval, PINP procollagen type I N terminal propeptide, sCTX serum C-terminal telopeptides, uNTX urinary N-terminal telopeptides, ALP alkaline phosphatase

It is evident that both anastrozole and letrozole cause a significant increase in the bone turnover markers studied here, and that these effects increase over time. Since both drugs have similar effects on bone metabolism and

turnover, there is a clear AI class effect on bone health in postmenopausal women with hormone-sensitive breast cancer. Tamoxifen has been reported to have some beneficial effects on bone turnover and fracture risk in

postmenopausal women [4, 20–22], but the results here show that these positive effects do not carry over once tamoxifen therapy is discontinued. Our study showed an increase in bone turnover that could eventually lead to bone loss. Patients who had previously received tamoxifen showed significantly greater increases in the bone turnover markers PINP, sCTX, uNTX and bone ALP compared with patients who had not been treated with tamoxifen. These results are similar to those from the ATAC trial, which suggested that bone resorption and formation are likely to be suppressed by about 30 and 15%, respectively, in patients treated with tamoxifen compared with an untreated population [23]. Prior tamoxifen therapy has also been shown to have a major effect on how AIs affect bone. This study has shown that prior treatment with tamoxifen profoundly increases the effects of AIs on bone turnover, and that these effects increase over time. Major increases in bone turnover are seen when tamoxifen is withdrawn and anastrozole or letrozole is started. These findings are similar to those seen in the IES bone substudy: in those patients who were on tamoxifen for 2–3 years and then switched to exemestane, there was a significant decrease in BMD compared with baseline within 6 months at both the lumbar spine (2.7%; $P < 0.0001$) and hip (1.4%; $P < 0.0001$) [24]. Thus, any benefit that tamoxifen has on bone density is lost after tamoxifen treatment ends and AIs begin. Therefore, patients who take anastrozole or letrozole after tamoxifen need the same bone monitoring as any patient taking anastrozole or letrozole alone.

In conclusion, these results indicate that the effects of anastrozole and letrozole on bone turnover are similar and increase with time. However, tamoxifen treatment has a major effect on how AIs affect bone.

Acknowledgments This research was supported by unrestricted educational grants from Novartis and Astra Zeneca. The authors thank all of the patients who entered this study.

References

- Howell A, Cuzick J, Baum M, ATAC Trialists' Group et al (2005) Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. *Lancet* 365:60–62
- Thurlimann B, Keshaviah A, Coates AS, The Breast International Group (BIG) 1–98 Collaborative Group et al (2005) A comparison of letrozole and tamoxifen in postmenopausal women with early breast cancer. *N Engl J Med* 353:2747–2757
- Osborne CK (1999) Aromatase inhibitors in relation to other forms of endocrine therapy for breast cancer. *Endocr Relat Cancer* 6:271–276
- Grey AB, Stapleton JP, Evans MC et al (1995) The effect of the antiestrogen tamoxifen on bone mineral density in normal late postmenopausal women. *Am J Med* 99:636–641
- Marttunen MB, Hietanen P, Tiitinen A et al (1998) Comparison of effects of tamoxifen and toremifene on bone biochemistry and bone mineral density in postmenopausal breast cancer patients. *J Clin Endocrinol Metab* 83:1158–1162
- Horwitz KB (1999) Bringing estrogen receptors under control. *Breast Cancer Res* 1:5–7
- McCloskey E, Hannon R, Lakner G et al (2007) Effects of third generation aromatase inhibitors on bone health and other safety parameters: results of an open, randomised, multi-centre study of letrozole, exemestane and anastrozole in healthy postmenopausal women. *Eur J Cancer* 43:2523–2531
- Coombes RC, Kilburn LS, Snowdon CF, Intergroup Exemestane Study et al (2007) Survival and safety of exemestane versus tamoxifen after 2–3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. *Lancet* 369:559–570 erratum in: *Lancet* 369:906
- Dixon JM, Renshaw L, Young O et al (2008) Letrozole suppresses plasma estradiol and estrone sulphate more completely than anastrozole in postmenopausal women with breast cancer. *J Clin Oncol* 26:1671–1676
- Riggs BL (2000) Are biochemical markers for bone turnover clinically useful in monitoring therapy in individuals osteoporotic patients? *Bone* 26:551–552
- Dowsett M, Jones A, Johnston SR et al (1995) In vivo measurements of aromatase inhibition by letrozole (CGS 20267) in postmenopausal patients with breast cancer. *Clin Cancer Res* 1:1511–1515
- Geisler J, King N, Dowsett M et al (1996) Influence of anastrozole (Arimidex), a selective, non-steroidal aromatase inhibitor, on in vivo aromatisation and plasma oestrogen levels in postmenopausal women with breast cancer. *Br J Cancer* 74:1286–1291
- Geisler J, Ekse D, Helle H et al (2006) Letrozole suppresses tissue and plasma estradiol, estrone and estrone sulphate more effectively compared to anastrozole. *Breast Cancer Res Treat* 199(suppl 1):S23–S24 Abstract 103
- Reid DM, Doughty J, Eastell R et al (2008) Guidance for the management of breast cancer treatment-induced bone loss: a consensus position statement from a UK Expert Group. *Cancer Treat Rev* 34(suppl 1):S3–S18
- Coates AS, Keshaviah A, Thurlimann B et al (2007) Five years of letrozole compared with tamoxifen as initial adjuvant therapy for postmenopausal women with endocrine-responsive early breast cancer: update of study BIG 1–98. *J Clin Oncol* 25:486–492
- Hillner B, Ingle JN, Rowan T et al (2003) American Society of Clinical Oncology 2003 update on the role of bisphosphonates and bone health issues in women with breast cancer. *J Clin Oncol* 21:4042–4045
- Brufsky A, Harker WG, Beck JT et al (2007) Zoledronic acid inhibits adjuvant letrozole-induced bone loss in postmenopausal women with early breast cancer. *J Clin Oncol* 25:829–836
- Bundred NJ, Campbell ID, Davidson N et al (2008) Effective inhibition of aromatase inhibitor-associated bone loss by zoledronic acid in postmenopausal women with early breast cancer receiving adjuvant letrozole: ZO-FAST study results. *Cancer* 112:1001–1010
- Hadji P, Body JJ, Aapro MS et al (2008) Practical guidance for the management of aromatase inhibitor-associated bone loss. *Ann Oncol* 19:1407–1416
- Chang J, Powles TJ, Ashley SE et al (1996) The effect of tamoxifen and hormone replacement therapy on serum cholesterol, bone mineral density and coagulation factors in healthy postmenopausal women participating in a randomised, controlled tamoxifen prevention study. *Ann Oncol* 7:671–675
- Seeman E (2002) Pathogenesis of bone fragility in women and men. *Lancet* 359:1841–1850
- Fisher B, Costantino JP, Wickerham DL et al (2005) Tamoxifen for the prevention of breast cancer: current status of the National

- Surgical Adjuvant Breast and Bowel Project P-1 study. *J Natl Cancer Inst* 97:1652–1662
23. Eastell R, Hannon RA, Cuzick J, on behalf of the ATAC Trialists' group et al (2006) Effect of an aromatase inhibitor on BMD and bone turnover markers: 2-year results of the Anastrozole, Tamoxifen, Alone or in Combination (ATAC) trial. *J Bone Miner Res* 8:1215–1223
 24. Coleman RE, Banks LM, Kilburn LS, on behalf on the Intergroup Exemestane Study (IES) group (2007) 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: a randomised controlled study. *Lancet* 8:119–127