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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

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ABSTRACT

Given potential differences between the skeletal and other effects of the third generation aromatase inhibitors (AIs), we conducted an open, randomised Phase I study, comparing the effects of three licensed AIs on bone turnover markers, lipid profiles and adrenal function.

Treatment comparisons were undertaken in 90 healthy postmenopausal women with normal bone mineral density who received once daily oral anastrozole (1 mg, $n = 29$), letrozole (2.5 mg, $n = 29$) or exemestane (25 mg, $n = 32$) for 24 weeks with a subsequent 12 week washout period.

All three AIs induced increases in bone resorption markers, but no significant differences were observed in their effects on bone turnover markers. Greater differences were observed in lipid metabolism. Notably, exemestane, but not anastrozole or letrozole, significantly increased the LDL:HDL cholesterol ratio by 12 weeks, largely mediated by a decrease in HDL-cholesterol.

Further, long-term clinical studies are required to determine the impact, if any, of the differences observed between the AIs.

1. Introduction

Aromatase inhibitors (AIs) prevent oestrogen biosynthesis in peripheral tissues by inhibiting the cytochrome P450 enzyme, aromatase, which catalyses the conversion of adrenal androgens (androstenedione and testosterone) to oestrogens (oestrone and oestradiol). The third-generation agents comprise the non-steroidal, competitive inhibitors, anastrozole and letrozole, and the steroidal, non-competitive inhibitor exemestane. Improved efficacy and tolerability compared to tamoxifen has resulted in recommendation of their use in the treatment of early breast cancer.[1,2] Pre-clinical and clinical studies suggest that there may be differences between these agents in the skeletal, cardiovascular and endocrine systems. Limited pre-clinical data with exemestane suggested that this agent might stimulate bone formation,[3] but clinical trial data

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report all three agents to increase fracture risk to a similar extent.[4] The interpretation of clinical studies is complicated as the comparator is usually tamoxifen, a treatment demonstrated to have relatively weak beneficial effects on bone turnover and fracture risk.[5,6] While it would be desirable to conduct head-to-head studies of AIs with fracture rate as the primary outcome, such studies would entail several thousand participants with many years of follow-up. Increased bone turnover markers and decreases in bone mineral density (BMD) are well established risk factors for incident fractures and can be used as surrogate measures. We have undertaken a comparator study of all three currently used AIs to determine if there are any significant differences in the effect of these agents on bone turnover in normal postmenopausal women. Additionally, we wished to compare their effects on lipid profiles and static and dynamic adrenal function.

2. Materials and Methods

2.1. Study design

This was a multi-centre, open, randomised study to assess surrogate safety parameters of the approved clinical doses of anastrozole, letrozole and exemestane. Subjects were enrolled from four centres in two countries: the United Kingdom ($n = 2$) and Hungary ($n = 2$). The study aimed to recruit 120 healthy postmenopausal women. They were eligible for inclusion in the study if at least 4 years postmenopausal, with normal bone mineral density (BMD) at the spine and hip defined as a T-score $\geqslant 1$ by WHO criteria,[7] a normal resting electrocardiogram (ECG), a resting blood pressure $\leqslant 160/90$ mmHg, resting heart rate <90 bpm and a BMI between 18 and 34 inclusive. Exclusion criteria included use of hormone therapy within the last year; known lipid disorders; uncontrolled hypertension, diabetes or hypothyroidism; fractures within the last 6 months; bilateral hip replacement; chronic renal or liver impairment; asthma treated with regular medication; alcohol or drug abuse and use of any regular medication or therapy known to affect sex hormone status, lipid profiles, bone turnover or adrenal function. During the study, participants were required to abstain from taking any new prescribed medication, where possible, including over the counter products and grapefruit or grapefruit juice.

2.1.1. Baseline assessments

Baseline assessments included bone specific alkaline phosphatase (bone ALP), total cholesterol, triglycerides, low-density lipoprotein-cholestrol (LDL-C), estimated high-density lipoprotein-cholestrol (HDL-C), cortisol, aldosterone and fasting glucose. BMD was assessed by dual energy X-ray absorptiometry (DXA) of the total hip and lumbar spine to determine volunteer eligibility using Lunar (GE Lunar Corp., Madison, WI) or Hologic (Hologic Corp., Bedford, MA) devices. Serum oestradiol was measured using the high-sensitivity assay described by Dowsett et al.[8]

2.2. Treatment

Eligible participants were randomised to receive once daily oral dosing of 1 mg anastrozole, 2.5 mg letrozole or 25 mg exemestane for a period of 24 weeks with follow-up thereafter for a further 12 weeks (i.e. a period of 36 weeks from study start; Fig. 1). A 24-week dosing period was chosen to allow sufficient time for the bone biomarkers to stabilise.[9,10]

2.3. Outcome assessments

Biochemical markers were measured at baseline (two visits), 12, 24 and 36 weeks. The primary objective of this study was to compare the changes in bone ALP between baseline and 24 weeks for the three AIs. Secondary objectives were to compare the effects on another biochemical marker of bone formation, serum collagen type I amino-terminal propeptide (PINP), the resorption marker serum β C-terminal crosslinking telopeptide of type I collagen (βCTX) and serum intact parathyroid hormone (PTH) as an index of calcium flux to and from bone. A repeat DXA scan was also performed at the 24 weeks assessment. Another secondary objective was to compare the effect of the three agents on lipid profiles and adrenal function. Lipid profiles included serum total cholesterol, triglycerides, HDL-C (calculated retrospectively), LDL-C and the apolipoproteins Apo A-I and Apo B. Adrenal function tests included levels of serum cortisol, aldosterone, androstenedione, testosterone, 17-hydroxyprogesterone, dihydroepiandrostenedione (DHEA) and serum DHEA sulphate. Dynamic adrenal function was also assessed by ACTH stimulation tests at baseline, 12, 24, and 36 weeks. A dose of 1 μg of Tetracosactrin dissolved in 1 mL of saline was administered as a single intravenous injection. Serum samples for cortisol, aldosterone, androstenedione, testosterone, DHEA, 17-hydroxyprogesterone and serum DHEA sulphate were obtained immediately before the injection and at 30 min and 60 min after administration. Pre-stimulation adrenal insufficiency was defined as either having a cortisol less than

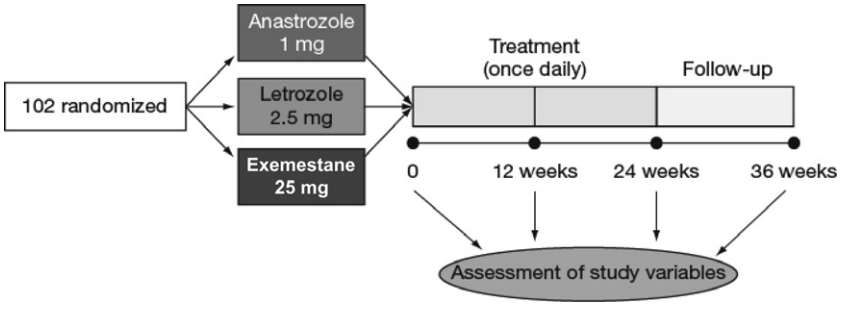

Fig. 1 – Overview of the design of the LEAP study.

200 nmol/L or having an aldosterone less than 55 pmol/L. Post ACTH stimulation adrenal insufficiency is defined as having a peak cortisol less than 500 nmol/L.

Blood samples were collected after a 10-h overnight fast at baseline and weeks 12, 24 and 36 for the bone markers, lipid and endocrine measurements. Serum samples were stored at −70 °C until analysis while plasma samples for oestradiol and lipids were stored at −20 °C. Analysis of all measurements was carried out under blinded conditions.

Bone ALP was measured in singlicate by a paramagnetic chemiluminescent method on an Acess® autoanalyser (Beckman Coulter Inc., USA). The interassay CV was 5.9% at 11.8 μg/L. PINP was measured by radioimmunoassay in duplicate (Orion Diagnostics Oy, Finland). The interassay CV was 3.7% at 42.4 μg/L and the intraassay CV was 4.0%. Serum βCTX was measured in duplicate by ELISA (Nordic Bioscience Diagnostics A/S, Denmark). The interassay CV was 8.4% at 0.097 μg/L and the intraassay CV was 6.7%. Serum intact PTH was measured in duplicate by ELISA (Biomerica Inc, USA) with an interassay CV of 7.1% at 3.3 pmol/L and the intraassay CV was 3.0%. All samples from an individual were measured in the same analytical batch.

2.4. *Ethics approval*

This study was conducted in accordance with the Declaration of Helsinki and in a manner consistent with Good Clinical Practice and applicable regulatory requirements. The final study protocol, the Written Informed Consent Forms and all advertising materials were approved by the local research ethics committee or research board. Each investigator was responsible for informing the committees or boards of any amendment to the protocol in accordance with local requirements.

2.5. *Sample size and statistical analysis*

Based on a standard deviation in log-transformed bone ALP of 0.228 at 6 months observed in the anastrozole tamoxifen alone or in combination (ATAC) trial of anastrozole,[10] 28 subjects in each group would give 80% power at the 5% significance level to detect a difference between treatments of 0.174 (corresponding to a difference of approximately 16–19% between groups) in the change from baseline of log-transformed bone ALP. To allow for dropouts, the sample size was increased to 40 in each treatment arm but recruitment was discontinued early when the dropout rate was found to be much lower than anticipated. The primary analysis population consisted of those subjects who completed the 24-week treatment period.

For each of the main outcome variables the baseline was the average of two values recorded prior to treatment, unless only one measurement was available. Since not normally distributed, values of bone ALP and the variables relating to bone formation, resorption, lipid metabolism and adrenal function were log-transformed prior to analysis using an analysis of covariance (ANCOVA) model. In addition to treatment and baseline values, terms for baseline BMI, smoking and time since last menstrual period were included in the model as these factors can influence rates of bone turnover.

Results are presented in terms of percentage change (derived from geometric least squares means, GLSMs) from baseline, along with associated 95% confidence intervals and *p*-values for the overall treatment comparison and all pairwise comparisons. Due to the exploratory nature of this study no adjustment was made for multiple comparisons.

Simple linear regression was employed to examine the relationship between changes in bone turnover and baseline serum oestradiol or baseline BMI. In an exploratory retrospective analysis, two uncoupling indices were derived to describe the treatment effects on markers of formation and resorption jointly.[11] One index was computed as the difference between βCTX and BAP Z-scores, and the second as the difference between βCTX and PINP Z-scores. The Z-scores were calculated as the log-transformed biomarker measurements, normalised using the baseline mean and standard deviation of the baseline measurement of that biomarker, across the three treatment arms. The uncoupling indices were analysed using the ANCOVA model with terms for treatment and baseline values of the uncoupling index, smoking status, BMI and log-transformed oestradiol.

Changes in lumbar spine and total hip BMD *T*-scores were compared in a retrospective non-parametric analysis, using Wilcoxon signed rank test for pair-wise comparisons and the Kruskal–Wallis test for the overall comparison.

3. Results

One hundred and two subjects were randomised to treatment (anastrozole: 34; letrozole: 34; exemestane: 34). Of these, 96 subjects received study treatment, and 90 (88.2%) subjects completed 24 weeks of study treatment (anastrozole: 29 [85.3%]; letrozole: 29 [85.3%]; exemestane: 32 [94.1%]) and were included in the primary analysis population.

Of the six women who received treatment but were excluded from the primary analysis, three discontinued study treatment before 24 weeks due to adverse events (letrozole $n = 1$ and exemestane $n = 1$) or unwillingness to continue the study (letrozole $n = 1$). The other three subjects (one in each group) were excluded due to protocol deviations (hypothyroidism; less than 4 years postmenopausal and past use of an oestrogen implant). Overall, the treatment groups were well balanced for major demographic characteristics (Table 1) including age, years since menopause and history of hysterectomy and oophorectomy.

3.1. *Effects on bone turnover*

In the primary analysis population, bone ALP, βCTX, PINP or PTH values were similar at entry to the study between the three groups (Table 2). Changes in all four analytes at 12, 24 and 36 weeks are given in Table 3 and the changes over the 24 weeks of treatment exposure are shown in Fig. 2. Treatment with all three AIs was associated with small numerical increases in bone ALP over 24 weeks, with the changes in the exemestane group achieving statistical significance. There were, however, no statistically significant differences in the change from baseline between the groups ($p = 0.469$) (Fig. 2). With the second bone formation marker, serum PINP, statistically significant increases from baseline were observed in all

Table 1 – Baseline characteristics of the 96 women randomised in the study and who initiated treatment with one of the aromatase inhibitors

	Anastrozole	Letrozole	Exemestane
n	30	32	34
Age (year) (mean, SD)	60 ± 8	59 ± 6	58 ± 8
Height (cm) (mean, SD)	161 ± 6	164 ± 5	163 ± 6
Weight (kg) (mean, SD)	76 ± 12	76 ± 10	74 ± 10
BMI (kg/m^2) (mean, SD)	29 ± 3	29 ± 4	28 ± 3
Years since menopause (year)			
⩽4 (*n*)	1	3	1
4–10 (*n*)	14	17	22
11–15 (*n*)	8	6	5
>15 (*n*)	7	6	6
Prior hormone therapy, *n*	9	11	13
Hysterectomy, *n*	10	7	9
Bilateral oophorectomy, *n*	3	1	2
Smoking, *n*	3	7	7

Table 2 – Baseline biochemical measurements in the 90 women randomised within the study and who completed all 24 weeks of the assigned treatment (primary analysis population)

	Anastrozole	Letrozole	Exemestane
n	29	29	32
Bone biochemistry (median, range)			
Bone ALP, μg/L	12, 8–23	13, 9–25	13, 7–27
βCTX, μg/L	0.5, 0.1–1.0	0.5, 0.2–1.2	0.5, 0.2–1.2
PINP, μg/L	42, 19–78	40, 20–117	45, 19–93
PTH, ng/L	63, 26–223	58, 26–130	60, 31–120
Lipid profile (mean ± SD)			
Total cholesterol, mmol/L	5.6 ± 0.8	5.6 ± 1.0	5.4 ± 0.8
Triglycerides, mmol/L	1.3 ± 0.5	1.4 ± 0.6	1.4 ± 0.7
LDL cholesterol, mmol/L	4.1 ± 0.8	4.2 ± 1.0	4.0 ± 0.8
HDL cholesterol, mmol/L	1.5 ± 0.4	1.4 ± 0.4	1.5 ± 0.4
LDL/HDL ratio	2.5 ± 1.0	2.7 ± 0.9	2.7 ± 0.9
Apo B/Apo A-I ratio	0.6 ± 0.2	0.6 ± 0.2	0.6 ± 0.2

Table 3 – Percentage changes from baseline for markers of bone metabolism in the primary analysis population

Variable/ time point	% change derived from geometric least squares mean (95% CI)			Treatment comparison *p*-value			
	Anastrozole	Letrozole	Exemestane	A versus L	A versus E	L versus E	Overall
Bone ALP (weeks)							
12	−2.9 (−8.1, 2.7)	1.6 (−3.5, 6.9)	2.7 (−2.1, 7.8)	0.189	0.099	0.731	0.224
24	2.0 (−4.3, 8.6)	2.9 (−2.9, 9.1)	6.6 (0.8, 12.7)	0.809	0.252	0.351	0.469
36	3.0 (−3.8, 10.2)	11.6 (4.9, 18.8)	14.5 (7.9, 21.6)	0.056	0.012	0.523	0.035
PINP (weeks)							
12	−1.1 (−8.3, 6.6)	3.2 (−3.6, 10.6)	10.5 (3.4, 18.0)	0.347	0.017	0.129	0.054
24	13.6 (3.0, 25.4)	11.3 (1.8, 21.8)	23.4 (13.2, 34.5)	0.732	0.171	0.078	0.178
36	12.4 (2.1, 23.6)	17.0 (7.1, 27.7)	33.9 (23.1, 45.7)	0.491	0.003	0.018	0.008
βCTX (weeks)							
12	13.8 (1.0, 28.3)	25.9 (12.9, 40.3)	12.1 (1.0, 24.4)	0.169	0.829	0.100	0.207
24	16.4 (2.7, 31.9)	27.8 (14.0, 43.3)	23.0 (10.3, 37.3)	0.220	0.469	0.600	0.468
36	15.0 (4.3, 26.8)	23.8 (13.3, 35.3)	20.2 (10.4, 30.9)	0.215	0.459	0.602	0.460
PTH (weeks)							
12	4.8 (−3.8, 14.1)	−0.2 (−7.7, 8.0)	−11.1 (−17.5, −4.1)	0.355	0.002	0.024	0.007
24	−7.7 (−18.0, 4.0)	−10.7 (−19.9, −0.4)	−20.5 (−28.4, −11.8)	0.648	0.042	0.100	0.095
36	9.5 (−1.3, 21.4)	2.8 (−6.5, 13.0)	−0.7 (−9.3, 8.8)	0.319	0.127	0.575	0.304

Treatment was discontinued at 24 weeks.

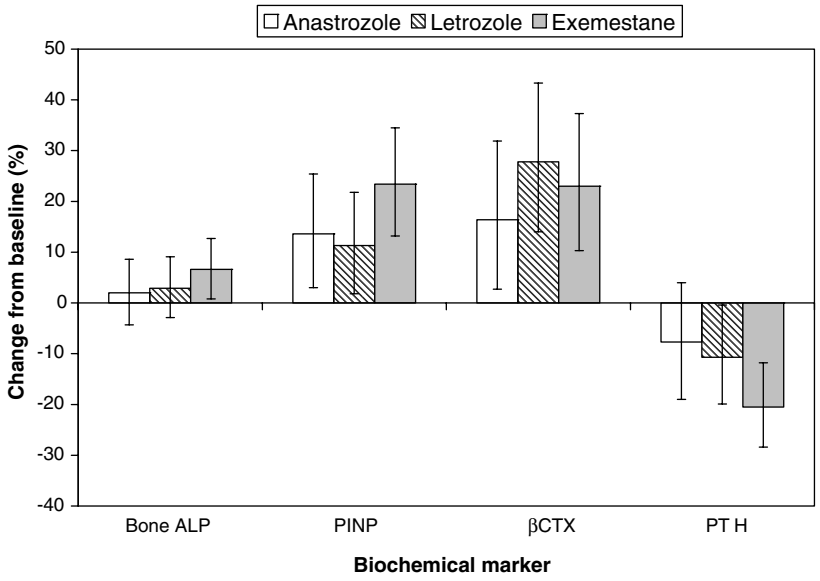

Fig. 2 – Changes in biochemical markers of bone turnover and PTH between baseline and 24 weeks (end of treatment) in the primary analysis population. No overall statistical differences were observed between the three groups (see Table 3).

treatment groups, but again there were no significant differences between the inhibitors ($p = 0.718$, Table 3, Fig. 2). Serum βCTX was also statistically significantly increased after 24 weeks of all AIs (Fig. 2) with statistically similar changes observed in all three groups ($p = 0.6847$ for between groups comparison, Table 3). Finally, all three AIs decreased serum levels of PTH at 24 weeks, though the change in the anastrozole group did not reach statistical significance (Fig. 2). The effects of the inhibitors on serum PTH were not statistically significant between the treatment groups ($p = 0.095$), but the decrease following exemestane was significantly greater than that observed during anastrozole ($p = 0.042$) (Table 3). The uncoupling index, derived from changes in the bone resorption markers (serum βCTX) and changes in either of the bone formation markers (PINP or bone ALP) showed no significant differences between the three agents after 24 weeks of therapy (Fig. 3). When derived from serum βCTX and bone ALP, the index was positive with all agents (resorption > formation), while the use of serum PINP suggested that changes in resorption and formation rates were less disparate (Fig. 3).

Baseline BMI correlated with pre-treatment circulating endogenous oestradiol ($r = 0.28$, $p = 0.007$) and both BMI and oestradiol negatively correlated with baseline serum βCTX ($r = -0.32$, $p = 0.0025$ and $r = -0.35$, $p = 0.0007$, respectively) and PINP ($r = -0.30$, $p = 0.004$ and $r = -0.26$, $p = 0.016$, respectively). As the changes in biochemical markers of bone resorption and formation during treatment were similar, the three groups were pooled for analysis of the relationship between baseline BMI, oestradiol and changes in biochemical markers. Baseline BMI and oestradiol were significantly correlated with the increase in serum βCTX ($r = 0.26$, $p = 0.015$, Fig. 4, and $r = 0.23$, $p = 0.032$, respectively) and BMI also correlated significantly with the increase in serum PINP ($r = 0.23$, $p = 0.030$). Changes in the biochemical markers, but not PTH,

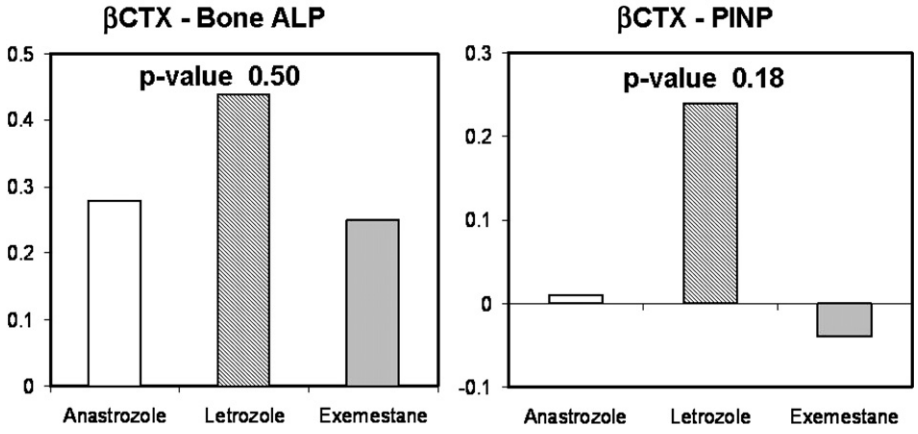

Fig. 3 – Uncoupling indices between baseline and 24 weeks derived using changes in z-score of serum βCTX as the resorption marker and changes in z-score of serum bone ALP or PINP as formation markers (see text for details). Higher values indicate a preponderance of resorption over formation. No statistical differences were observed between the three groups.

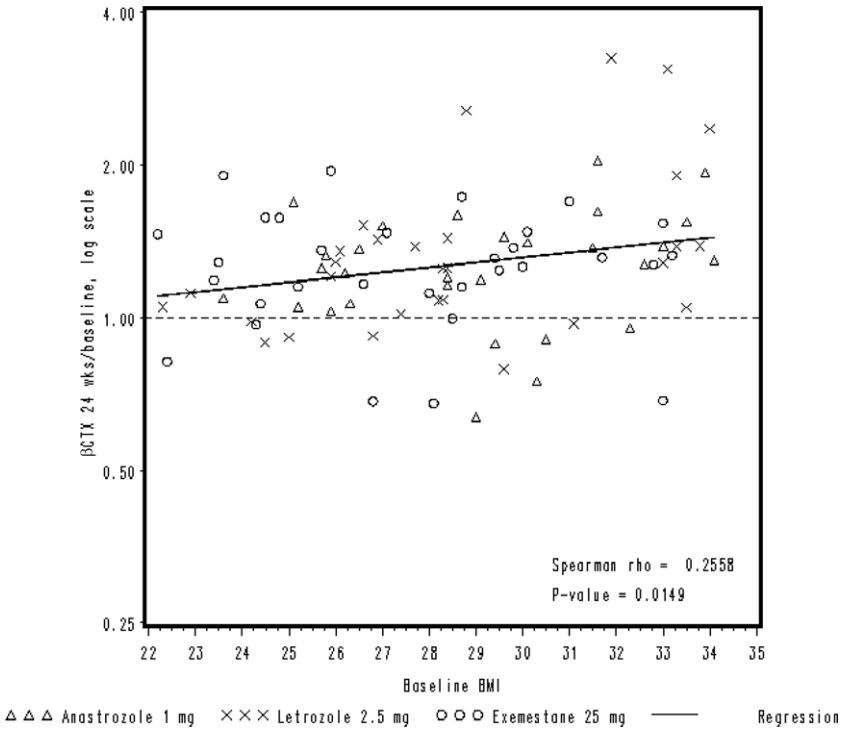

Fig. 4 – Correlation between changes in serum βCTX between baseline and 24 weeks (expressed as the 24 week to baseline ratio) and BMI at entry to the study.

appeared to persist 12 weeks after cessation of treatment (Table 3). Retrospective non-parametric analysis of change in BMD did not detect any significant differences between the treatment arms.

3.2. *Effects on lipid metabolism*

Total cholesterol and other lipid measurements were similar at entry to the study in the three groups (Table 2).

Exemestane, but not the other AIs, was associated with a statistically significant decrease in total cholesterol at 12 weeks (Table 4) but differences between the groups were not statistically significant ($p = 0.535$). A similar pattern was observed at 24 weeks ($p = 0.308$; Table 4, Fig. 5). In contrast, significant differences were observed in changes from baseline in the LDL-C/HDL-C ratio between the three groups at 12 weeks ($p = 0.019$) and 24 weeks ($p = 0.047$) (Fig. 5). Compared with the non-steroidal agents, exemestane was associated with statistically significant increases from baseline in LDL-C/HDL-C ratio at 12 and 24 weeks $p = 0.0464$ and $p = 0.007$ versus anastrozole and $p = 0.045$ and $p = 0.025$ versus letrozole, respectively (Table 4, Fig. 5). The increased LDL-C/HDL-C ratios during exemestane therapy resulted from a significant decrease in HDL-C rather than an increase in LDL-C (Table 4, Fig. 5). Statistically significant differences between the groups were also observed for changes in Apo B/Apo A-1 ratios at 12 weeks ($p = 0.028$) and 24 weeks ($p = 0.020$) (Table 4, Fig. 5) with exemestane again differing from the other two AIs. Exemestane was associated with significant increases in Apo B/Apo A-I ratio while this ratio remained unchanged in the other two groups. These changes in atherogenic ratios and HDL-C returned to baseline after 12 weeks of treatment (Table 4). Triglyceride measurements showed wide variability and letrozole was associated with an early increase in serum triglycerides compared with the other two AIs at 12 weeks (overall $p = 0.011$; $p = 0.037$ versus anastrozole and $p = 0.004$ versus exemestane), an effect that did not persist at the 24-week assessment (Table 4, Fig. 5). There were no observed differences between the three AIs for the other lipid measurements assessed.

3.3. *Effects on adrenal function*

At 24 weeks, there were no measurable changes from baseline in adrenal function as assessed by the rise in ACTH-stimulated cortisol at 15, 30 and 60 min post-stimulation. Similarly, with the exception of the rise in aldosterone at 60 min following ACTH stimulation, where there was a greater rise with letrozole (e.g. LSMean change +118 versus −23 versus anastrozole, $p = 0.0247$) there were no differences in adrenal response (cortisol or aldosterone) at 24 weeks compared to baseline between the three groups.

3.4. *Adverse events*

A total of 69 (72%) subjects reported at least one adverse event; most frequently hot flushes (anastrozole: 23%, letrozole: 22% and exemestane: 24%]), and nasopharyngitis (anastrozole 17%, letrozole: 13% and exemestane: 15%). A total of 28 (29%) subjects had at least one adverse event considered by the investigator to be due to study medication (exemestane $n = 11$; anastrozole $n = 9$ and letrozole $n = 8$). Five subjects had a serious adverse event; one on anastrozole (suprapatellar bursitis), one on letrozole (cerebral contusion, subarachnoid

Table 4 – Percentage changes from baseline in lipid variables in the primary analysis population. Treatment was discontinued at 24 weeks

Variable/time point	Least squares mean % change (95% CI)			Treatment comparison *p*-value			
	Anastrozole	Letrozole	Exemestane	A versus L	A versus E	L versus E	Overall
Total cholesterol (weeks)							
12	−2.4 (7.0, 2.3)	−3.7 (−8.1, 0.6)	−5.5 (−9.7, −1.3)	0.628	0.267	0.524	0.535
24	0.3 (−4.7, 5.4)	0.0 (−4.7, 4.7)	−3.9 (−8.5, 0.7)	0.912	0.173	0.202	0.308
36	−0.6 (−6.4, 5.2)	2.3 (−3.1, 7.7)	1.7 (−3.5, 6.9)	0.417	0.512	0.872	0.692
Triglycerides (weeks)							
12	−2.9 (−12.6, 6.7)	9.6 (0.5, 18.7)	−7.7 (−16.5, 1.0)	0.037	0.417	0.003	0.011
24	0.2 (−13.7, 14.1)	5.3 (−7.7, 18.4)	2.3 (−10.4, 14.9)	0.546	0.807	0.711	0.829
36	−6.7 (−23.4, 10.1)	10.7 (−4.9, 26.4)	8.0 (−7.2, 23.2)	0.092	0.154	0.783	0.196
HDL-C (weeks)							
12	−1.8 (−7.7, 4.1)	−3.5 (−9.0, 2.1)	−10.4 (−15.9, −4.8)	0.637	0.021	0.055	0.047
24	−0.3 (−6.3, 5.8)	−2.9 (−8.6, 2.8)	−13.9 (−19.6, −8.3)	0.483	<0.001	0.003	<0.001
36	0.5 (−6.1, 7.0)	1.8 (−4.4, 7.9)	−1.7 (−7.9, 4.4)	0.751	0.588	0.378	0.672
Ratio LDL:HDL (weeks)							
12	0.0 (−7.2, 7.2)	−3.1 (−9.8, 3.7)	8.8 (2.3, 15.4)	0.488	0.046	0.007	0.019
24	4.6 (−5.5, 14.6)	3.4 (−6.0, 12.8)	17.0 (7.9, 26.1)	0.847	0.045	0.025	0.047
36	1.7 (−5.8, 9.1)	−1.3 (−8.2, 5.7)	4.1 (−2.6, 10.9)	0.520	0.586	0.225	0.477
Non-HDL (weeks)							
12	−2.8 (−8.1, 2.6)	−4.1 (−9.1, 0.8)	−3.5 (−8.3, 1.3)	0.676	0.830	0.835	0.916
24	1.3 (−5.2, 7.8)	1.2 (−4.9, 7.3)	−0.5 (−6.3, 5.3)	0.987	0.654	0.661	0.875
36	−0.6 (−7.4, 6.3)	2.3 (−4.1, 8.7)	3.3 (−2.8, 9.4)	0.493	0.356	0.812	0.633
Ratio Apo B: Apo A I (weeks)							
12	−1.0 (−5.9, 3.8)	−3.2 (−7.7, 1.2)	4.4 (0.1, 8.7)	0.458	0.067	0.009	0.028
24	0.0 (−6.4, 6.4)	−0.8 (−6.7, 5.2)	9.0 (3.3, 14.7)	0.842	0.022	0.012	0.020
36	−3.7 (−9.7, 2.4)	−2.0 (−7.7, 3.6)	−2.0 (−7.4, 3.4)	0.662	0.649	0.988	0.877

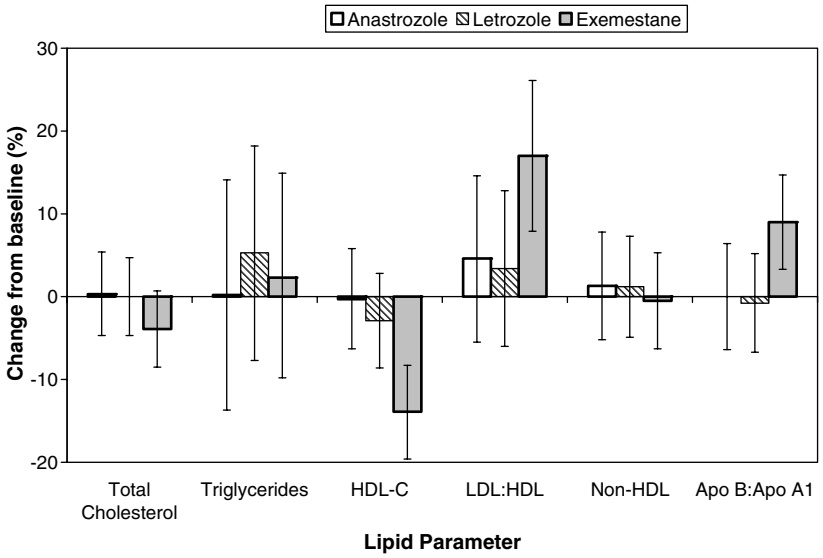

Fig. 5 – Changes in lipid measurements and indices between baseline and 24 weeks (end of treatment) in the primary analysis population. Changes in HDL-C, LDL:HDL and Apo B:Apo A-1 induced by exemestane were significantly different to those induced by anastrozole or lettrozole (see Table 4).

haemorrhage and vertigo) and three on exemestane (respiratory infection, acute haemorrhagic gastritis and laryngeal pachydermy). None were considered by the investigator to be due to study medication.

4. Discussion

The results of this study demonstrate that, despite the same enzymatic target, anastrozole, letrozole and exemestane have

different pharmacodynamic properties, consistent with previous observations.[12] While there has been much focus on the potential for different effects on bone turnover, particularly given the androgen-like structure of the metabolites of exemestane, the present study suggests that greater differences may be observed in non-skeletal tissues, particularly with regard to cholesterol metabolism. Adrenal function seems to be unaffected by the use of these AIs.

Low postmenopausal levels of oestradiol are associated with increases in bone turnover markers and increased fracture rates.[13,14] The present study shows all three AIs to have similar effects on biochemical markers of bone formation and resorption, and thus bone turnover, with increases in bone ALP, PINP and βCTX and a decrease in PTH. Similar changes were observed in previous studies where changes in bone markers associated with individual AIs were compared with each other, or placebo.[9,15–17] PTH secretion is responsive to the level of plasma-ionised calcium, varying inversely, and a decrease in PTH is an expected consequence of an increase in bone resorption greater than that in bone formation. The observation of a similar or greater decrease in PTH with exemestane suggests that the increased efflux of calcium from bone is at least as great as with other AIs, and does not support the hypothesis that exemestane may be more bone-sparing.

While our study showed no apparent detrimental effect of any of the agents on adrenal function, it remains important to determine their long-term safety as their use increases in women with potentially curable breast cancer. Cardiovascular disease, particularly coronary heart disease and stroke, remains the leading cause of morbidity and mortality in postmenopausal women.[18] As in men, increasing total cholesterol and specifically LDL-C are related to cardiovascular morbidity and mortality in women,[19] though women tend to have higher levels of protective HDL-C. Some studies have suggested that low HDL-C, particularly high total cholesterol/HDL-C ratio, could be a more significant risk factor for females than for males, whereas total cholesterol is less important for women.[20] Elevated triglycerides have been suggested to be a stronger predictor of cardiovascular diseases in women.[21] Finally, high apolipoprotein levels have been associated with an increased risk both in women and men.[22] The cardiovascular safety of AIs has recently been reviewed.[23,24] Nabholtz and Gligorov concluded that all three AIs had a significantly lower risk of thromboembolic events compared with tamoxifen. The lipid measurements in the current study suggest an increase in atherogenic ratios with exemestane treatment. Whilst AI treatments have been associated with changes in serum lipid profile, the clinical consequence of these changes, if any, have not been demonstrated in long-term adjuvant trials to date.

In summary, this randomised, comparative study demonstrates that anastrozole, letrozole and exemestane have similar effects on bone, but that differences between the three agents are observed in non-skeletal tissues, particularly with regard to changes in atherogenic ratios. Further investigation of the AIs is required to determine if these differences are of clinical significance in the long-term management of early breast cancer.

Clinical trial registration number

Phase 1 study. EudraCT number 2004-000436-89.

Conflicts of interest statement

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