Effect of exemestane on the lipidemic profile of post-menopausal operable breast cancer patients following 5–7 years of adjuvant tamoxifen: preliminary results of the ATENA substudy

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Long-term endocrine therapy for breast cancer may have clinical implications as drugs that potentially alter the lipid profile may increase the risk of developing cardiovascular disease. In this study, a companion subprotocol to the ATENA (Adjuvant post-Tamoxifen Exemestane versus Nothing Applied) trial, we compared the effect of the steroidal aromatase inactivator exemestane on the lipid profile of post-menopausal women with operable breast cancer in the adjuvant setting to that of observation alone following deprivation of 5–7 years primary treatment with tamoxifen. In this open-label, randomized, parallel group study, 340 post-menopausal patients with operable breast cancer who had been treated with tamoxifen for 5–7 years were randomized to either 5 additional years of exemestane (25 mg/day; $n=172$) or observation alone ($n=168$). Assessments of total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and total serum triglycerides (TRG) were performed at baseline, and at 6 and 12 months. Total TRG levels were significantly reduced compared with baseline for the exemestane and the observational arm. Both total cholesterol and LDL levels were significantly increased above that of baseline values by 6 months, maintained through to 12 months, with no significant difference between the two treatment arms. There was no significant alteration observed for HDL over time or between the two arms. We conclude that sequential adjuvant treatment with exemestane in post-menopausal operable breast cancer patients following cessation of 5–7 years of tamoxifen does not appear to significantly alter the lipidemic profile for at least 12 months compared with an observational arm. *Anti-Cancer Drugs* 16:879–883 © 2005 Lippincott Williams & Wilkins.

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Introduction

Estrogen deprivation of the tumor is an established method of treating breast cancer. Chemoprevention utilizing tamoxifen has been shown to prevent the development of breast cancer in women at an increased risk [1]; however, its use in recent years has been questioned following indication of an increased risk of endometrial cancer, thromboembolic events and tolerability concerns [2]. More recently, inhibition of aromatase, the enzyme that converts androgens to estrogens, with agents including anastrozole, letrozole and exemestane, has been shown to be an effective alternative to tamoxifen for post-menopausal women with hormone-dependent breast cancer.

Exemestane is an irreversible steroidal inhibitor of aromatase [3,4] that has recently been shown to confer a disease-free survival advantage when given after 2–3 years of tamoxifen compared with the standard 5 years of tamoxifen in the adjuvant treatment of post-menopausal breast cancer patients [5].

Although estrogens remain a therapeutic target for breast cancer, they also possess additional physiological functions including involvement in bone and lipid metabolism, and cardiovascular, cognitive and sexual functions [6]. Due to the high levels of estrogen deprivation caused by aromatase inhibitors, the effects of such inhibition on bone mineral density, lipid profiles and thus cardiovascular disease [7,8] have been a concern, especially considering the protective effects that tamoxifen exerts on lipid profiles [9,10].

Extending tamoxifen use further to the standard 5-year duration of treatment has been proven to be ineffective [11]. Post-menopausal women with hormone

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receptor-positive tumors who have completed about 5 years of adjuvant tamoxifen therapy should be considered for treatment with an aromatase inhibitor, as this has been shown to be effective by the early results of the MA17 trial with letrozole [12]. The use of aromatase inhibitors in the extended adjuvant setting is a very promising option. There is, however, a question about the long-term safety of these agents; in particular, with respect to the effects on the lipidemic profiles of post-menopausal women. However, in our opinion, this effect should not be compared with that of tamoxifen, which is known to be beneficial. In this extended adjuvant treatment setting, the effect of aromatase inhibition on lipids should be compared with the post-tamoxifen deprivation lipidemic profile, which is probably, after a certain period of time, in the ranges of the average post-menopausal female population.

As a substudy to the ATENA (Adjuvant post-Tamoxifen Exemestane versus Nothing Applied) trial examining 5 years of exemestane versus observation in post-menopausal operable breast cancer patients treated in the adjuvant setting with 5–7 years of tamoxifen, we aim to examine alterations in the lipid profile following initiation of exemestane treatment in comparison to that of women who cease tamoxifen treatment and thus lose the beneficial effect of tamoxifen on the lipid profile.

Patients and methods

The ATENA phase III randomized parallel-group multicenter trial is designed to compare 5 years of adjuvant exemestane versus 5 years of observation in post-menopausal women with operable breast cancer who have received 5–7 years of adjuvant tamoxifen. Recruitment of 1803 core patients is planned in the ATENA trial from study sites of the Hellenic Breast Surgeons Society. The primary endpoint for the core protocol is disease-free survival (DFS). The current substudy was designed to evaluate changes in the patients' serum lipid profile during study treatment. This is a preliminary report on the analysis of data from 340 post-menopausal patients randomized to receive exemestane (25 mg/day; $n = 172$) or observation alone ($n = 168$). Exemestane treatment was planned for 5 years unless disease relapse or excessive toxicity was documented, the patient refused further treatment or any new anti-cancer therapy was initiated.

This study enrolled women with histologically confirmed stage I–IIIA primary adenocarcinoma of the breast, with estrogen and/or progesterone receptors positive or unknown, who have undergone surgery with a curative intent. Patients must have completed at least 5 years and not more than 7 years of continued treatment with tamoxifen (20 mg/day), while tamoxifen could have been discontinued up to 6 months prior to study entry. Absence of any evidence of local or distant metastatic disease was required prior to randomization.

Concomitant hormonal medication such as hormone replacement therapy within the last 4 weeks prior to study entry, or raloxifen or any other selective estrogen receptor modulator, or treatment with steroids for more than 2 weeks or hormonal treatment with any other agent apart from tamoxifen prior to randomization was not allowed. Patients with clinical evidence of severe osteoporosis were not allowed to enter the trial, while treatment with bisphosphonates or calcitonin was permitted. No other concomitant anti-cancer medication, chemotherapy, radiotherapy or investigational agent was allowed during the study. Treatment was discontinued if this was the physician's decision or the patient's wish. Study treatment was also discontinued in the case of disease recurrence or second primary cancer. Finally, treatment was discontinued in the case of severe toxicity or consent withdrawal.

All patients entering the substudy had no history of any concomitant disease that could affect the lipid profile, including familial dyslipidemia. Also, there were no reports of cholesterol-lowering agent consumption in our concomitant medication database.

Patients were not instructed to follow a specific diet during the study; however, before offering a blood sample all patients were required to fast for 12 h. Blood samples for lipid profile analysis [cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL) and total serum triglycerides (TRGs)] were measured at baseline and then during each follow up visit, performed at either 6 or 12 months according to the standard clinical practice at each participating center.

The study was approved by local institutional ethics committees and conducted according to the Declaration of Helsinki. Informed consent forms were signed by all patients before entering randomization.

Statistical analysis

Baseline characteristics including age, prior adjuvant chemotherapy and radiotherapy are summarized. Summary statistics of all lipid variables are based on measures of central tendency and dispersity (mean, median, standard deviation, percentiles and range) according to treatment group for each visit. In addition to absolute values, median percentage changes from baseline are provided. Most comparisons were based on median percentage changes from baseline values of all lipid parameters. This was considered as the most reliable method for comparison as it allowed for the comparison of measurements within the same patients over the study period, instead of evaluating changes of the absolute

values for each parameter. This was considered as the most efficient method in order to overcome intervariability within the groups of patients. The distribution of percentage change was tested against the two treatment groups by Mann–Whitney *U*-test as data deviate from normality. Baseline characteristics were compared by either χ^2- or *t*-tests. All tests were two sided with a level of significance set at 5%.

Results

So far, 448 patients have been randomized in the ATENA trial. Among these, 340 patients were eligible for this lipid analysis—172 in the exemestane arm and 168 in the observation arm. Patient characteristics are summarized in Table 1; there were no statistically significant differences between the groups.

Changes of the median absolute values for each lipid parameter over the study period are shown in Table 2. Median percentage changes from baseline values of all lipid parameters, evaluating changes within the same patients over the study period are shown in Table 3.

Overall there was a trend for increasing cholesterol levels in both treatment arms (Tables 2 and 3). These increases were statistically higher than the baseline values by 6 and 12 months (Table 3); however, there were no differences between the two arms (Tables 2 and 3). There was also a statistically significant increase in the LDL levels for both groups compared with baseline through to 12 months. By 12 months the exemestane arm demonstrated a statistically significant increased level of LDL compared with the observational arm (Table 2).

Total TRG levels were consistently decreased below the baseline levels throughout the study in both arms (Tables 2 and 3).

There was no statistically significant alteration in the HDL levels in either arm compared with baseline (Table 3). At 12 months only, the exemestane arm demonstrated a statistically significant decreased level of HDL compared with the observational arm (Table 2).

Table 1 Patient characteristics

Characteristic	Exemestane	Observation
Number [*n* (%)]	172 (50.6)	168 (49.4)
Mean age [years (range)]	63.3 (40–81)	62.6 (39–82)
Weight before randomization [kg (range)]	72.0 (48–100)	69.8 (52–100)
Prior chemotherapy [*n* (%)]		
yes	58 (33.72)	58 (34.52)
no	111 (64.53)	107 (63.69)
missing data	3 (1.74)	3 (1.78)
Prior local radiotherapy [*n* (%)]		
yes	92 (53.48)	79 (47.02)
no	69 (40.11)	75 (44.64)
missing data	11 (6.39)	14 (8.3)
ECOG [*n* (%)]		
0	131 (76.16)	118 (70.23)
1	25 (14.53)	36 (21.42)
2	1 (0.58)	0 (0)
not reported	15 (8.72)	14 (8.33)
Histopathologic type [*n* (%)]		
Infiltrating ductal	127 (73.83)	127 (75.59)
Infiltrating lobular	14 (8.13)	16 (9.52)
Other	19 (11.04)	11 (6.54)
Not classified	12 (6.97)	14 (8.33)
Histopathologic grade [*n* (%)]		
G1	23 (13.37)	24 (14.28)
G2	88 (51.16)	76 (45.23)
G3	34 (19.76)	39 (23.21)
not applicable (due to lobular type)	14 (8.13)	16 (9.52)
missing data	13 (7.56)	13 (7.74)
Surgery [*n* (%)]		
mastectomy	76 (44.18)	80 (47.61)
wide local excision	86 (50.0)	78 (46.42)
type of surgery not specified	10 (5.81)	10 (5.95)
Axillary nodes [*n* (%)]		
positive	67 (34.35)	71 (38.37)
negative	102 (52.30)	97 (52.43)
missing data	19 (9.74)	10 (5.40)
no axillary dissection	7 (3.58)	7 (3.78)
ER and PR status [*n* (%)]		
ER+/PR+	84 (48.3)	90 (53.57)
ER+/PR–	15 (8.72)	16 (9.52)
ER–/PR+	9 (5.23)	9 (5.35)
ER+/PR unknown	13 (7.55)	10 (5.95)
ER and PR unknown	41 (29.7)	43 (25.59)

Discussion

Extending treatment with exemestane following several years of adjuvant tamoxifen does not appear to differ significantly from the effect of tamoxifen deprivation (observation alone) in terms of lipid profile, indicating that exemestane is not adversely detrimental to lipidemic parameters. This study indicates that there is an overall trend for increasing cholesterol levels matched by increasing LDL and decreasing TRG levels following cessation of tamoxifen. HDL levels in the exemestane arm did not increase as rapidly as seen in the observational arm; however, levels never altered significantly from baseline values. Our results confirm the lack of any effect on HDL levels in both arms previously reported in other trials [12–14].

The TEAM (Tamoxifen and Exemestane Adjuvant Multicenter) trial is a phase III randomized parallel-group multicenter trial which is organized as a single study consisting of eight separate managed country-specific trials with nine participating countries. TEAM is designed to compare 5 years of adjuvant exemestane versus 5 years of tamoxifen in post-menopausal women with early breast cancer. A Greek substudy assessing the effect on the lipidemic profile has recently reported interim results which are consistent with our present finding [13].

Since it is generally accepted that tamoxifen exerts a beneficial effect on lipid profiles, possibly as a result of its agonistic estrogenic activity, estrogen deprivation caused

Table 2 **Serum lipid profiles: changes of the median absolute values [mg/dl (range)] for each parameter over the study period**

	Baseline			6 months			12 months		
	Exemestane	Observation	*p*	Exemestane	Observation	*p*	Exemestane	Observation	*p*
Cholesterol	215 (145–307)	213.5 (117–294)	*0.685*	231 (160–294)	223 (136–341)	*0.767*	226.5 (150–330)	231.0 (156–357)	*0.785*
HDL	57 (31–85)	56 (33.8–239)	*0.587*	57 (38–94)	60 (42–80)	*0.170*	52 (34–86)	59 (41–87)	*0.029*
LDL	139.4 (74–209)	133 (53.8–216)	*0.567*	157 (81–221)	145 (56–230)	*0.340*	160 (82–258)	146.5 (13–198)	*0.011*
TRG	118 (40–520)	123 (36–546)	*0.780*	112 (36–402)	121 (45–294)	*0.657*	112.5 (44–224)	101 (50–240)	*0.560*

Table 3 **Median percentage changes from baseline values of all lipid parameters over the study period**

		6 months			12 months		
		Exemestane	Observation	p^*	Exemestane	Observation	p^*
Cholesterol		+6.2	+8.0	*0.803*	+8.9	+9.2	*0.488*
	p^+	*0.021*	*0.004*		*0.006*	*0.001*	
HDL		−0.9	+6.4	*0.054*	+2.6	+9.7	*0.266*
	p^+	*0.214*	*0.144*		*0.887*	*0.285*	
LDL		+11.1	+11.2	*0.716*	+10.3	+9.7	*0.606*
	p^+	*0.017*	*0.008*		*0.01*	*0.01*	
TRG		−20.6	−8.9	*0.862*	−20.1	−14.7	*0.469*
	p^+	*0.054*	*0.022*		*0.001*	*0.01*	

p^* = comparison between the two arms of the study at the same time point.
p^+ = comparison of each arm to baseline.

by aromatase inhibitors has raised some concerns with respect to serum lipid profile and bone metabolism. However, considering that exemestane is an irreversible steroidal aromatase inactivator requiring *de novo* enzyme synthesis for estrogen synthesis, exemestane and its metabolites have been suggested to have a protective effect on lipid metabolism compared with the non-steroidal aromatase inhibitors [15–17]. Exemestane is currently under investigation in several clinical studies in the adjuvant setting. Recent data from the IES (Intergroup Exemestane Study) trial randomizing early breast cancer patients to tamoxifen for 2–3 years and then either tamoxifen or exemestane for the remainder of the 5-year period indicated that exemestane following tamoxifen was superior to tamoxifen alone in terms of disease-free survival in post-menopausal women with hormone-responsive primary breast cancer [5,18]. Concerns about tamoxifen resistance and some support for a reduced incidence of contralateral breast cancer indicate that sequential treatments strategies may be the way forward [5]. This was also suggested from the recently prematurely terminated NCIC CTG-MA17 study [12] examining the effectiveness of 5 years of letrozole in post-menopausal women with breast cancer who had completed 5 years of tamoxifen therapy. More recently, the Cancer Policy and Clinical Affairs section of the American Society of Clinical Oncologists has concluded that the adjuvant therapy for post-menopausal women with hormone receptor-positive breast cancer should include an aromatase inhibitor in order to lower the risk of tumor recurrence, either as initial therapy or after treatment with tamoxifen [19]. Currently, there are various ongoing studies examining the role of exemestane in a variety of settings attempting to determine the appropriate sequence and duration of exemestane in adjuvant endocrine therapy of breast cancer [18,20].

Other potentially protective effects of aromatase inhibitor over tamoxifen treatment have become evident from the ATAC (Anastrozole, Tamoxifen, Alone or in Combination) trial [21]. Although using a non-steroidal aromatase inhibitor (anastrozole), the authors observed fewer cardiovascular and thromboses events in the aromatase inhibitor group, and there was no report of adverse effect of anastrozole on the lipid profile [21,22]. Since aromatase inhibitors are now being investigated not only in the metastatic, but also in the adjuvant setting, their effects on several estrogen-dependent functions in other tissues apart from the breast are currently under investigation.

In a study of lipidemic parameters, Atalay *et al.* reported that exemestane decreased while tamoxifen increased TRG levels over time [22]. This finding is consistent with our data. Of the few currently published studies, there is additional support for our data indicating that exemestane has no obvious detrimental effects on serum lipid profiles in post-menopausal metastatic breast cancer patients. There are in fact strong indications that it may have a beneficial effect on TRG levels, which may possibly contribute to a reduction in coronary artery disease in a population already at increased risk [23–25]. If TRG levels are indeed a predictive factor for heart disease, the reduction in TRG levels following administration of exemestane warrants further investigation. There is also evidence that lower TRG levels below the

'threshold' value of about 1.5 mmol/l (133 mg/dl) will cause a change in the LDL size profile to larger, less dense and, therefore, less atherogenic species [24]. In this context, the statistically significant increase in the LDL levels observed at 12 months in the group of patients treated with exemestane should be considered of lesser clinical importance since it is accompanied by a significant decrease in the TRG levels.

This study is the first to prospectively evaluate the effects of exemestane versus observation following discontinuation of 5–7 years of adjuvant tamoxifen on serum lipid profiles in the adjuvant setting. Any beneficial effect of exemestane in terms of survival remains to be confirmed. However, our report provides evidence that switching to exemestane following tamoxifen does not appear to be detrimental to the lipidemic parameters studied here.

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