Lipid changes in breast cancer patients on exemestane treatment: final results of the TEAM Greek substudy

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Background: The Greek substudy of the Tamoxifen and Exemestane Adjuvant Multicenter International trial compared the effect of exemestane on the lipid profile of postmenopausal, breast cancer patients to that of tamoxifen in the adjuvant setting.

Patients and methods: Lipidemic profile changes were studied in 142 postmenopausal patients randomized to receive either adjuvant exemestane (n = 77) or tamoxifen (n = 65). Total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL) and serum triglyceride (TRG) levels were measured at baseline and then every 3 months for the first 12 months of treatment and at 18 and 24 months.

Results: A trend for a reduction in TC was found in both treatment arms; however, TC and LDL levels were consistently and significantly decreased in tamoxifen arm only. The mean HDL level was higher for the tamoxifen arm compared with the exemestane arm across time. No significant trend was detected throughout the study period on TRG levels on either arm.

Conclusions: Unlike tamoxifen’s beneficial effect on TC and LDL levels, exemestane appears to have a neutral effect on lipidemic profile of postmenopausal, breast cancer patients. These data offer additional information with regard to the safety and tolerability of exemestane treatment in the adjuvant setting.

Key words: aromatase inhibitors, breast cancer, cholesterol, exemestane, lipids, tamoxifen, TEAM trial

Introduction

Breast cancer remains the most common type of cancer in females in the developed countries. Approximately two-thirds of breast tumors are estrogen dependent and blockade of estrogen through both receptor antagonism and inhibition of synthesis offers ideal targets for therapy [1, 2].

Tamoxifen, a selective estrogen receptor modulator (SERM), remained for years the cornerstone of endocrine therapy for breast cancer, following the first demonstration of efficacy ~25 years ago [3]. However, although in general is well tolerated, the toxicity profile of tamoxifen has raised concerns over the years, particularly considering the increased risk of thromboembolism, vasomotor symptoms and endometrial cancer [4].

In the last few years, inhibition of aromatase, the enzyme that converts androgens to estrogens, has been investigated as an alternative to tamoxifen for postmenopausal women with hormone-dependent breast cancer [5]. A number of major, phase III randomized clinical trials have assessed third-generation aromatase inhibitors (AIs) (anastrozole, letrozole and exemestane) in the adjuvant treatment of postmenopausal women as an option for initial therapy or sequential use after 2.5 or 5 years treatment with tamoxifen [6–9]. Results of all those trials provided solid evidence of the important role that AIs play in the adjuvant treatment of postmenopausal women, questioning the role of tamoxifen as the ‘gold standard’. AIs are now regarded by many to be the standard of care for adjuvant therapy of hormone receptor-positive primary breast cancer after menopause. However, there are still many important and unresolved questions that need to be addressed including the optimal time of AI treatment initiation, duration of the therapy and the associated long-term toxic effects and risks in relation to the subsequent high level of estrogen deprivation in patients under treatment with AIs [10].

Even though estrogens pose a therapeutic target for breast cancer, they are also known to have physiological activity on bone and lipid metabolism, cardiovascular, cognitive and sexual functions [11]. In fact, estrogen deprivation in postmenopausal women has been associated with altered plasma lipid profiles, increased bone fracture and cardiovascular disease [12]. Although it is generally accepted that tamoxifen, possibly as a result of its agonistic estrogenic activity, exerts a protective effect on lipid profile [13, 14], there are still limited data regarding the effect of estrogen deprivation by AIs on serum lipid levels. Furthermore, assessing the impact of AIs on lipid profile is rather difficult as tamoxifen was the comparator in most trials with the exception of MA17, where letrozole was compared with placebo [7].
The effects of long-term aromatase inhibition will be an important factor in determining the usefulness of AIs. Since there is an increased risk of cardiovascular disease, osteoporosis and diabetes [15] in postmenopausal women, it is essential to study the consequences of estrogen removal, especially when AIs are considered for long-term use in both the adjuvant and chemopreventive settings.

Exemestane is an irreversible steroidal inactivator of aromatase [16, 17] and has been shown to inhibit the enzyme by ~98% in vivo [18].

In a study by Engan et al. [19], which examined the lipid profile in postmenopausal metastatic breast cancer (MBC) patients receiving exemestane or tamoxifen, significant reductions in total cholesterol (TC), triglyceride (TRG), high-density lipoprotein (HDL) and Apo A1 levels were observed following 12 weeks of treatment with exemestane. In another prospective, randomized phase II study, the EORTC trial 10951, examining serum lipid profiles in postmenopausal MBC patients, Atalay et al. [20] reported that exemestane and tamoxifen had opposite effects on TRG levels; exemestane lowered while tamoxifen increased TRG levels over time. In their study of 122 women, lipid parameters (TC, TRG, HDL, Apo A, Apo B and Lip a) were monitored at 8, 24 and 48 weeks of treatment. Apart from TRG and Apo A1, no other lipid parameters were altered during the study for either treatment arm. The authors concluded that since their population was relatively small and many patients did not have data at the latter time points, a larger population should be studied to confirm the results. Hypercholesterolemia was not reported in the Intergroup Exemestane Study (IES) trial of sequential exemestane after tamoxifen [9, 21]. In another study examining the lipid profiles in 55 postmenopausal women with early breast cancer who switched to exemestane after at least 2 years of tamoxifen treatment, TRGs and HDL cholesterol significantly decreased in the exemestane group, while low-density lipoprotein (LDL) cholesterol significantly increased at the end of the 1-year study period [22].

In a placebo-controlled study involving 147 postmenopausal women with early breast cancer, exemestane had no major effect on lipid profile except for a modest but significant decrease from baseline in HDL cholesterol (P = 0.001) and apolipoprotein A1 [23]. Similar results were found by our group when we compared the lipid profiles of early breast cancer patients who have already received tamoxifen for 5–7 years and then stopped for observation with those patients who continued to receive five additional years of exemestane as part of the Adjuvant post Tamoxifen Exemestane versus Nothing Applied trial. The study concluded that sequential adjuvant treatment with exemestane in postmenopausal 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 [24].

This report presents the final analysis at 2 years of the lipid profile substudy, a Greek subprotocol of the Tamoxifen and Exemestane Adjuvant Multicenter (TEAM) trial, which is examining exemestane treatment for 5 years compared with sequential therapy with 2.5–3 years tamoxifen followed by exemestane for a total of 5 years, as adjuvant treatment for postmenopausal women with early breast cancer. All data presented here are corresponding to lipid profile analysis of patients’ blood samples obtained through the first 2-year period of the TEAM study, before patients in the tamoxifen treatment arm of the protocol switching to Exemestane.

patients and methods

patients

The TEAM phase III randomized, international multicenter trial began in 2001 and patients were enrolled in nine different countries, being Belgium, France, Germany, Greece, Ireland, Japan, Netherlands, UK and the United States. It was originally designed as an ‘upfront’ treatment strategy trial, comparing 5 years of adjuvant exemestane versus 5 years of tamoxifen in postmenopausal women with early breast cancer. Following the results of IES [9], which showed that patients who switched to exemestane after 2.5–3 years tamoxifen had significant improvement of disease-free survival (DFS) and significant reduction in risk of contralateral breast cancer, the TEAM trial protocol was thus amended to evaluate sequential therapy with 2.5–3 years tamoxifen followed by exemestane for a total of 5 years compared with exemestane for 5 years. A number of substudies are also being run independently in participating countries aiming to assess different study parameters, mainly concerning long-term safety effects. The TEAM trial has recruited 9775 patients worldwide—211 patients recruited in Greece by the Hellenic Breast Surgeons Society (HBSS)—and each substudy is running on the basis of the individualized study parameters. Coprimary end points for the core protocol are DFS at 2.75 years (comparison of upfront treatment with exemestane versus tamoxifen) and 5 years (tamoxifen to exemestane sequential strategy versus exemestane) and the secondary end points are overall survival, new primary breast cancer and safety issues.

The Greek substudy was designed to evaluate changes in the patients’ serum lipid profile during the first 2 years of study treatment. The sample size for the substudy was determined by the overall TEAM study, Greece originally offered to participate with 150 patients in the TEAM trial as this number was decided to be feasible for the Greek centers running various protocols with AIs that period. Following the amendment of the TEAM core protocol in 2004 and increase of the total number of patients of TEAM, the number of patients from Greece also increased and reached 211 patients until closure of enrolment in Greece at the end of 2005. As some centers from Greece did not participate in the lipid substudy, only 176 patients eligible for the lipid study signed informed consent at the same time with the parent study randomization and were enrolled in the substudy.

This is a report on the final analysis of data from 142 postmenopausal patients with at least two measurements for all four lipid parameters randomized to receive exemestane (25 mg/day; n = 77) or tamoxifen (20 mg/day; n = 65) for 2.5–3 years or until disease relapse, excessive toxicity, patient refusal for further treatment or the start of any new anticancer therapy. Nevertheless, a sample size of 142 is sufficient for detecting an effect size of 0.5 (standardized difference, μ1 − μ2/σ) with power of 80%, for a two-sided test at the 5% level of significance as described in the statistical section.

This study enrolled women with histologically confirmed primary adenocarcinoma of the breast who had undergone surgery with a curative intent and who met the following criteria: estrogen receptor- and/or progesterone receptor-positive tumor with a size of >3 cm, or any lymph node positive (N+), or tumor size <3 cm, N0 and one of the following factors: mitotic activity index >10 mitotic figures/field or tumor grade III (Bloom–Richardson). Patients were required to have adequate hematological, renal and hepatic function (defined as platelets > 100 × 10^9/L,
white blood cell $> 3 \times 10^9/\text{l}$, creatinine $< 1.5 \text{ mg/dl}$, aspartate aminotransferase or alanine aminotransferase $< 45 \text{ IU/L}$ (international units per litre) and an Eastern Cooperative Oncology Group performance status of 0, 1 or 2). They were required to be available for follow-up for the duration of the trial and signed informed consent was mandatory before study entry. The study was approved by local institutional ethics committees and conducted according to the Declaration of Helsinki.

Patients were not allowed any hormone replacement treatment at least for 4 weeks before randomization into the TEAM trial; this was an exclusion criterion of the core protocol. Cholesterol-lowering agent consumption was not allowed in patients enrolled in the lipid substudy and there were no such reports in our concomitant medication database.

Following a 12-h fast, blood samples were analyzed for lipid profile (TC, HDL, LDL and TRGs) and were measured at baseline, every 3 months for a period of 12 months and then at 18 and 24 months under treatment.

statistical analysis

Assuming compound symmetry, i.e., that the observations made at time $t$ on a particular individual have a correlation $\rho$ with observations made at time $t'$ and this correlation is assumed the same for all values $t$ and $t'$, provided $t \neq t'$. Assuming $\rho = 0.50$ and the availability on the average of three observations per individual after baseline, to guarantee a power 80% to detect an effect size of 0.5, at a two-sided $\alpha = 0.05$, the required number is $0.417 \times 64 \times 2 = 54$ patients [25].

Summary statistics of all lipid variables are presented [mean, standard deviation (SD)] for each visit. Mixed-effects models, with intercept as fixed effect and compound symmetry variance–covariance matrix, were used to explore the differential treatment effect of exemestane and tamoxifen across time for each of the four lipid parameters. Time is measured in months from baseline.

The polynomial growth curve models used, by taking into account the within-subject variability and the problem of missing values commonly present in repeated measures data, are reliably exploring trends across time and between treatment groups. The mixed-effects models were run both on the actual lipid parameter values and their logarithms. Estimation of absolute value means and mean changes from baseline for each treatment arm at each time point obtained from the appropriate mixed-effects models are presented. Analysis was carried out using the SAS statistical package. All reported $P$ values are two sided and results were considered significant at $\alpha = 0.05$.

**results**

Two hundred and eleven patients from Greece were randomized in TEAM trial core protocol from January 2001 to November 2005, with 110 patients randomized to the exemestane arm (E) and 101 patients to the tamoxifen arm (T). One hundred and forty-two postmenopausal patients from 9 of 18 centers of HBSS participating in the lipid substudy had at least two measurements for all four lipid parameters and were included in the present analysis (77 in E and 65 in T). Ninety-eight patients had lipid measurements at 18 months (51 in E and 47 in T) and 77 patients at 24 months or later (39 in E and 38 in T). Overall, 22 patients discontinued treatment due to recurrence (10), death of other cause (three), serious side-effects (six), new primary breast cancer (one) or refused to continue treatment (two) and did not reach the 24-month study period.

Mean observed absolute values and corresponding SDs for each lipid parameter at baseline, at 1 year, at 1.5 and 2 years after baseline are presented in Table 1, while mean observed changes from baseline values over the study period are presented in Table 2. The corresponding mean absolute values and mean changes from baseline over the study period as

### Table 1. Observed absolute values for lipid parameters (mg/dl) across the study period (mean ± standard error)

<table>
<thead>
<tr>
<th></th>
<th>Cholesterol value</th>
<th>HDL value</th>
<th>LDL value</th>
<th>Total triglycerides value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>E</td>
<td>T</td>
<td>E</td>
<td>T</td>
</tr>
<tr>
<td>Baseline</td>
<td>228 ± 5.9</td>
<td>232 ± 5.1</td>
<td>56 ± 2.0</td>
<td>58 ± 2.2</td>
</tr>
<tr>
<td>12 months</td>
<td>220 ± 5.8</td>
<td>201 ± 3.9</td>
<td>52 ± 1.9</td>
<td>58 ± 1.9</td>
</tr>
<tr>
<td>18 months</td>
<td>220 ± 6.3</td>
<td>211 ± 6.2</td>
<td>53 ± 1.7</td>
<td>55 ± 1.8</td>
</tr>
<tr>
<td>24 months</td>
<td>216 ± 6.2</td>
<td>199 ± 5.3</td>
<td>52 ± 1.8</td>
<td>57 ± 1.8</td>
</tr>
</tbody>
</table>

HDL, high-density lipoprotein; LDL, low-density lipoprotein; E, exemestane; T, tamoxifen.

### Table 2. Observed changes from baseline values over the study period (mean ± SE)

<table>
<thead>
<tr>
<th>Change from baseline</th>
<th>3 months</th>
<th>12 months</th>
<th>18 months</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SE</td>
<td>P</td>
<td>Mean ± SE</td>
<td>P</td>
</tr>
<tr>
<td>Cholesterol change</td>
<td>E −4.5 ± 4.8</td>
<td>NS</td>
<td>−13.1 ± 5.6</td>
<td>0.020</td>
</tr>
<tr>
<td></td>
<td>T −8.2 ± 5.9</td>
<td>NS</td>
<td>−28.9 ± 4.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL change</td>
<td>E −2.6 ± 1.4</td>
<td>NS</td>
<td>−3.7 ± 2.2</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>T −0.1 ± 2.3</td>
<td>NS</td>
<td>0.9 ± 2.0</td>
<td>NS</td>
</tr>
<tr>
<td>LDL change</td>
<td>E 4.4 ± 5.3</td>
<td>NS</td>
<td>−7.7 ± 5.4</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>T −16.6 ± 7.1</td>
<td>0.020</td>
<td>−21.1 ± 6.5</td>
<td>0.030</td>
</tr>
<tr>
<td>Total triglycerides</td>
<td>E −10.0 ± 8.0</td>
<td>NS</td>
<td>−9.0 ± 11.2</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>T −21.2 ± 13.7</td>
<td>NS</td>
<td>13.4 ± 9.2</td>
<td>NS</td>
</tr>
</tbody>
</table>

Note: t-test $P$ values; NS, nonsignificant when $P > 0.05$.

SE, standard error; E, exemestane; T, tamoxifen; HDL, high-density lipoprotein; LDL, low-density lipoprotein.
estimated from the mixed-effects models are presented in Table 3.

Figure 1A–D shows by treatment arm the observed and the estimated mean values for each lipid parameter across time. Cholesterol was significantly decreased across time for both arms, but for the T arm more steeply and with an effect sustained even after the first year of treatment (P < 0.0001 and P = 0.0004 for time and time-squared effect, respectively; treatment group × time interaction P value = 0.016). The corresponding estimated differences between T and E in absolute changes from baseline were of increasing magnitude across time with negative values at 3 months equal to −1.91 mg/dl [standard error (SE) = 0.79, 95% confidence interval (CI) −3.46 to −0.36], at 12 months to −7.65 mg/dl (SE = 3.16, 95% CI −13.85 to −1.44), at 18 months to −11.47 (SE = 4.74, 95% CI −20.78 to −2.16) and at 24 months equal to −15.29 mg/dl (SE = 6.32, 95% CI −27.7 to −2.88). The mean cholesterol level estimated was significantly lower for the T arm compared with the E arm at the 18- (P = 0.020) and 24-month time point (P = 0.0087) (Figure 1A).

The HDL levels decreased significantly across time for both treatment arms with a reversal at the 24-month time point (P = 0.042 and P = 0.057 for time and time-squared effect, respectively; treatment group × time interaction P value = 0.10). The estimated mean HDL level was higher for the T arm compared with the E arm across time (mean difference = 5.06, SE = 1.95, P = 0.011) (Figure 1B). The decrease in HDL across time for both treatment arms is apparent in Figure 1B, where the observed means along with the estimated by the mixed-effects models means are plotted against time in 3-month intervals for the first year and every 6 months thereafter.

According to the mixed-effects model estimating the LDL time trajectory, a second-order statistically significant effect of time (negative first-degree effect, −1.32 × time, P = 0.0029; positive second-degree, +0.046 × time², P = 0.0073) and a statistically significant treatment group × time interaction were found (for the T arm, −0.78 × time, P = 0.0023). For the E arm, the combination of first- and second-degree effect of time leads quickly (~6 months) to a plateau in the estimated LDL means by the mixed-effects models. As can also be seen in Table 1, for the E arm, the observed mean absolute values for LDL do not suggest a significant fall over time. For the T arm, a steep statistically significant decrease is apparent from the beginning and is maintained through the 24-month time point (Figure 1C). The corresponding estimated differences between T and E in absolute changes from baseline were of increasing magnitude across time with negative values at 3 months equal to −2.34 mg/dl (SE = 0.76, 95% CI −3.85 to −0.84), at 12 months to −9.38 mg/dl (SE = 3.06, 95% CI −15.38 to −3.37), at 18 months to −14.06 (SE = 4.58, 95% CI −23.07 to −5.05) and at 24 months equal to −18.75 mg/dl (SE = 6.11, 95% CI −30.76 to −6.74). No significant trend was detected throughout the study period on TRG levels on either arm (P = 0.38 and P = 0.54 for treatment arm and time, respectively). Observed values show a variable behavior, increasing or decreasing, in adjacent time points. An almost flat line across time describes the TRG process for both treatment groups with a nonsignificant mean difference across time between T and E (8.28 ± 5.97, P = 0.38) (Table 3, Figure 1D). It must be noted that time and treatment group are kept in the mixed-effects models in Figure 1D only for illustration purposes, even though they were found to be not significant.

**Table 3.** Estimated absolute values changes for lipid parameters across the study period according to the mixed-effects model (mean ± SE)

<table>
<thead>
<tr>
<th></th>
<th>Cholesterol value</th>
<th>HDL value</th>
<th>LDL value</th>
<th>Total triglycerides value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T–E</td>
<td>T–E²</td>
<td>T–E</td>
<td>T–E²</td>
</tr>
<tr>
<td><strong>Baseline</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean ± SE</td>
<td>−2.42 ± 5.95</td>
<td>−7.41 ± 5.62</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>NS</td>
<td>NS</td>
<td></td>
<td></td>
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<tr>
<td><strong>12 months</strong></td>
<td></td>
<td></td>
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<tr>
<td>Mean ± SE</td>
<td>−10.07 ± 5.5</td>
<td>−16.7 ± 5.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.070</td>
<td>0.0013</td>
<td>8.28 ± 9.57;</td>
<td></td>
</tr>
<tr>
<td><strong>18 months</strong></td>
<td></td>
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<td></td>
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<tr>
<td>Mean ± SE</td>
<td>−13.89 ± 5.93</td>
<td>−21.4 ± 5.52</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.020</td>
<td>0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>24 months</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SE</td>
<td>−17.72 ± 6.71</td>
<td>−26.16 ± 6.29</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>0.0087</td>
<td>&lt;0.0001</td>
<td></td>
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</tbody>
</table>

*constant difference between T and E across time.
SE, standard error; HDL, high-density lipoprotein; LDL, low-density lipoprotein; E, exemestane; T, tamoxifen.

**Discussion**

The present analysis of our data shows that adjuvant treatment with exemestane does not alter significantly the lipidemic profile of postmenopausal breast cancer patients. However, it seems that exemestane lacks the clear lipid-lowering effects of tamoxifen.

Assessing the impact of an AI on the lipid profile of postmenopausal patients is rather difficult in any trial where tamoxifen is the comparator. Tamoxifen, an SERM, is known to have lipid-lowering properties [26, 27]. On the other hand, during menopause and independently of their age, women experience adverse changes in their lipidemic parameters, including declines in concentrations of HDL cholesterol and increases in concentrations of TC, LDL cholesterol and TRGs [28, 29]. Therefore, in our opinion, the effect of AIs on the patients’ lipidemic profile should be compared with the lipidemic profile of the average postmenopausal female population [23, 30], taking also into account the therapeutic benefits of AIs observed in multiple clinical trials and in all treatment settings. However, it is also valid to compare lipid effects of AIs to tamoxifen as well because tamoxifen still remains the alternative drug choice and so the relative risks and benefits between the two drug choices are relevant.

In the present analysis of our study, TC levels were significantly decreased across time for both treatment arms, and this consistent trend for a reduction in TC was evident.
from the median percentage changes from baseline values reported in the preliminary analysis of our data [31]; however, this effect is steeper in the tamoxifen arm (Figure 1A).

Additionally, the mean HDL level estimated was higher for the tamoxifen arm compared with the exemestane arm across time (Figure 1B).

As to the LDL levels, those were decreased significantly across time for both arms, but with a sharper decrease for the tamoxifen arm (Figure 1C). An increase in LDL levels within the exemestane group of patients which was noticed at 3 and 6 months but not at later time points in the preliminary analysis of our data [31] was also confirmed here and appears to be an early and transient change as was originally reported, and thus, it is rather clinically not relevant.

A beneficial effect of exemestane on TRG levels reported in the preliminary analysis of our data [31] was not confirmed in the present, final analysis of 2 years under treatment as no significant trend was detected on TRG levels on either arm. Observed values showed a variable behavior, increasing or decreasing, in adjacent time points (Figure 1D) and our previous observation was probably due to variability and immaturity of the data.

Even though the effects of aromatase inhibition on lipids and on several estrogen-dependent functions in other tissues apart from the breast are under consideration mainly in the adjuvant therapy setting due to the long-term treatment period, the effect of AIs on the lipidemic profile has been under investigation since the early AI studies in MBC patients.

An early phase III study comparing letrozole to aminoglutethemide in postmenopausal women with MBC indicated that 3.8% of patients in the letrozole arm developed hypercholesterolemia [32]. A subsequent study in 20 postmenopausal women indicated a compromised lipid profile. Letrozole significantly increased serum TC, LDL, cholesterol, ApoB and TC : HDL ratio (atherogenic risk) compared with baseline [33]. However, no negative effects on lipid metabolism were reported by Harper-Wynne et al. [34] in a study of 32 healthy, postmenopausal women treated with letrozole. Similarly, there were no significant changes in lipid metabolic markers reported in a 6-month study of 42 healthy women randomly assigned to letrozole or placebo [35]. In another study by Wojtacki et al. [36], neither the AI letrozole nor anastrozole was found to negatively affect lipid parameters (TC, TRG, LDL and HDL) in 30 postmenopausal MBC patients.
Furthermore, in two randomized trials examining tamoxifen and anastrozole as first-line agents in MBC patients, anastrozole has so far shown no detrimental effects, while the effects of tamoxifen were consistent with previous reports [37–39]. Both vorozole [34] and fadrozole [40] have been studied with respect to their effect on lipid profiles, neither of which has shown any significant effect.

There are, however, significant differences between exemestane and the nonsteroidal AIs, anastrozole and letrozole, as exemestane is an irreversible aromatase inactivator and, as a result, de novo enzyme synthesis is required for estrogen synthesis. In addition, exemestane and its metabolites mimic androstenedione, reducing serum hormone-binding protein in a dose-dependent manner. As a result, it has been suggested that exemestane may have a protective effect on lipid metabolism [41–43]. In the randomized phase II EORTC trial 1095, examining serum lipid profiles in postmenopausal MBC patients, Atalay et al. [20] reported that exemestane and tamoxifen had opposite effects on TRG levels; exemestane lowered while tamoxifen increased TRG levels over time. We are presenting here similar results, however, as our data matured, an early change in TRG levels in favor of exemestane noticed in our preliminary report [31], was not confirmed in the present analysis. Additionally, in their study it is stated that 50% of patients had nonfasting lipid samples that could have affected the precision of their lipid measurements. In our study, all patients underwent lipid fasting for at least 12 h before their tests.

There are few currently published studies considering the effect of anastrozole and letrozole on serum lipid profiles of postmenopausal breast cancer patients under AIs treatment in the adjuvant setting. No effect of anastrozole on the lipid profile was observed in ATAC trial [6, 44]. However, conflicting results are seen in the ITA trial where lipid metabolism disorders were reported in 9.3% of patients treated with anastrozole and 4.0% receiving tamoxifen (P = 0.04) [45]. Another study which is examining the effects of letrozole on bone metabolism and parameters of cardiovascular risk is the prematurely terminated NCIC CTG-MA17 trial [7]. The MA.17 lipid substudy found that at 36 months compared with placebo, letrozole did not significantly alter lipid profile, including TRGs, LDL cholesterol, TC, HDL cholesterol and lipoprotein A [46]. In the Breast International Group 1–98 trial of initial adjuvant therapy, hypercholesterolemia was reported in 5.4% of the letrozole arm compared with 1.2% of the tamoxifen arm in patients with baseline values within normal limits, who then had an increase of 1.5 times the upper limit of normal [7].

Finally, an interesting study which recently reported preliminary findings provides indications on the differences among AIs considering their effect on lipidemic profile. The Letrozole, Exemestane and Anastrozole Pharmacodynamics trial is a direct comparison of the safety profiles between exemestane and the nonsteroidal AIs anastrozole and letrozole in 90 healthy postmenopausal women [47]. Preliminary results indicate that there are no significant differences between anastrozole and letrozole in the effects on LDL : HDL ratios, TRG concentrations and non-HDL concentrations. Exemestane seems to be associated with an increase in LDL : HDL ratio (+17) (P = 0.047) compared with anastrozole. There is no median change from baseline in total serum cholesterol for letrozole, a slight increase for anastrozole and a nonsignificant decrease for exemestane (−3.9) (P = 0.164 versus anastrozole). While evaluating these data, we need to take into consideration the small number of patients and the short follow-up.

This study is the first to prospectively evaluate the effects of exemestane versus tamoxifen on serum lipid profile in the adjuvant setting. The present final analysis of our data indicates that, unlike tamoxifen’s beneficial effect on TC and LDL levels, exemestane appears to have a rather neutral effect on lipidemic profile of postmenopausal, breast cancer patients. These data offer additional information to our knowledge on the safety and tolerability of exemestane treatment in the adjuvant setting.

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references


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