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Comparison of the Effects of Nonsteroidal and Steroidal Aromatase Inhibitors on Lipid Profile in Hormone-Sensitive Postmenopausal Early Stage Breast Cancer A Prospective, Open-Label, Single-Center, Randomized Controlled Trial

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Abstract

Research Question: Is there a significant difference in cumulative serum lipid events between nonsteroidal and steroidal aromatase inhibitors (AIs) in hormone-sensitive postmenopausal early stage breast cancer?

Background: Studies estimating the effect of AIs in post-menopausal early breast cancer have demonstrated conflicting results regarding the net changes in the composition of lipid profiles. To date, few studies have directly compared the effects of nonsteroidal and steroidal AIs on lipid metabolism.

Design: Lipidemic profile changes were studied in 34 post-menopausal patients randomized to receive either nonsteroidal AIs (n=18) or steroidal AI (n=16). Total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglyceride (TG) levels were measured at baseline and every 3, 6, and 12 months thereafter. The primary endpoint was cumulative incidence of serum lipid events.

Results: The cumulative incidence of serum lipid events at 12 months in the non-steroidal and steroidal arms was 66.67% and 68.75% respectively. The factors associated with serum lipid event were analyzed using univariate and multivariate analyses. In both analyses, LDL-C (HR-1.04, 95% 1.01-1.07; p-0.001) and TC were significantly associated with serum lipid event. There was no significant difference in the cumulative incidence of serum lipid events in either arm (HR, 0.69 95% 0.22-2.17; p-0.522).

Conclusion: Among post-menopausal hormone sensitive early breast cancer, no significant difference in cumulative serum lipid events at 1 year was observed in the steroidal or non-steroidal treatment arms. Importantly, the present study adds to the existing data that AIs significantly alter the mean TC, LDL, and HDL levels over time. Clinical trials investigating these changes in lipid profile and their impact on cardiovascular morbidity should be pursued.

Introduction

Aromatase inhibitors (AIs) have proven its superiority to tamoxifen in estrogen deprivation leading to survival benefit among postmenopausal women, hormone receptor positive breast cancer [1]. Consequently, AIs have been the preferred adjuvant therapy in hormone sensitive breast tumors as per National Comprehensive Cancer Network (NCCN), American Society of Medical Oncology (ASCO) and European Society Medical Oncology (ESMO) [2-4]. These AIs are used at least 5 years, and extended to 10 years in the adjuvant setting [5]. Indirect comparisons of the efficacy of the steroidal and non-steroidal AIs, when used in the adjuvant setting, suggested they are similar [6] However, owing to global estradiol deprivation, AIs have adverse cardiometabolic effects, which is likely modified by age, time from menopause, and the degree of preexisting cardiovascular disease [7] More importantly, estrogen deficiency in postmenopausal women has been shown to affect lipid metabolism [8]. Current data on AIs showing favorable, neutral, or unfavorable effect on different lipid parameters in various studies, do not allow drawing of any final conclusions about their effect on lipid metabolism [9]. Adverse effects on the lipid panel are not desirable as cholesterol and triglyceride concentrations are often used as a surrogate indicator for long term cardiovascular risk [10]. As the potential use of AIs expands beyond the context of adjuvant therapy for postmenopausal women diagnosed with breast cancer to chemoprevention for high risk women, consideration of risk benefit ratio is increasingly important [6].

Review of Related Literature

Incidence

In the Philippines, 20,627 new cases of breast cancer were reported in 2015. The incidence rate has been steadily rising since 1980, with an average annual percentage of 1.2% [11] with hormone receptor-positive breast cancer ranging from 59% to 69% [12]. A recent study of around 272 breast cancer patients found that two-thirds (65%) of the participants had positive hormonal receptor status and slightly more than half of the participants (51%) had positive Her2Neu status. In this study, almost 90% of the participants had early stage breast cancer and a good performance status, hence, aiming for the possibility of a cure [13].

In a review of 396 retired Philippine veteran-dependent breast cancer patients who received chemotherapy at the Veterans Memorial

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Medical Center from 2014 to 2019, 45% were hormone receptor-positive and 23% were hormone receptor-positive with concomitant Her2/neu receptors.

Aromatase inhibitors as standard of care

In postmenopausal women, aromatase inhibitors profoundly (>95%) inhibit aromatase, the rate limiting enzyme in the conversion of androgens to estradiol, causing "virtually complete" circulating estradiol deficiency, with reductions of plasma estradiol to <3 pmol/L, concentrations markedly below those measured in the natural menopause, typically ranging from 20 to 50 pmol/L [7]. Aromatase inhibitors are superior to Tamoxifen, with a modest improvement in 10 year-breast cancer mortality (12.1% versus 14.2%, relative risk, 0.85; 95% CI, 0.76-0.96, p=, 0.01) [7]. The current NCCN guidelines version, 3.2020, indicates that the preferred endocrine therapy option for post-menopausal women is aromatase inhibitor [2].

Several studies have evaluated AIs in the treatment of postmenopausal women with early stage breast cancer as initial adjuvant therapy, as sequential therapy following 2 to 3 years of tamoxifen, or as extended therapy following 4.5 to 6 years of tamoxifen. With a median of 100 months follow-up, 5216 postmenopausal women with HR-positive, early stage breast cancer enrolled in the ATAC trial demonstrated fewer recurrences (HR for DFS, 0.85; 95% CI, 0.76–0.94; P = .003) with anastrazole than with tamoxifen [14].

The BIG 1-98 is a randomized trial that tested the use of tamoxifen alone for 5 years, letrozole alone for 5 years, or tamoxifen for 2 years followed sequentially by letrozole for 3 years, or letrozole for 2 years followed sequentially by tamoxifen for 3 years. Among 8,010 women included in the analysis, disease-free survival was superior in letrozole-treated women (HR, 0.81; 95% CI, 0.70-0.93; log rank P = 0.003) [15].

The TEAM trial compared treatment of exemestane alone versus sequential therapy for 2.5 years to 3.0 years followed by exemestane to complete 5 years of hormone therapy. At the end of 5 years, 85% of patients in the sequential group and 86% in the exemestane group were disease-free (HR, 0.97%; 95 CI 0.88-1.08; P=0.60) [16].

The NCCN panel found no compelling evidence that there was a significant difference in efficacy or toxicity among the available aromatase inhibitors. All three showed similar antitumor efficacy and toxicity profiles in randomized studies in adjuvant settings [2]. However, owing to the high levels of estrogen deprivation caused by AIs, the effect of such inhibition on lipid profiles and cardiovascular disease (CVD) is a concern [9]. Because CVD is an important cause of death in older breast cancer survivors, accurate information on events associated with AIs is needed to inform clinical decision making. Unfortunately, the available evidence is mixed and inconclusive [17].

Aromatase inhibition and Lipid metabolism

To date, only a few studies have explored the lipid effects of AIs and conflicting results have been obtained, possibly owing to variations in trial design; in most trials, tamoxifen, with its known beneficial effect on lipids, was the comparator, while in others, the comparator was a placebo or healthy population, [9] or another aromatase inhibitor [18]. In the ATAC study, at a median follow up of 68 months, it was reported that anastrozole-treated patients had a greater incidence of hypercholesterolemia than tamoxifen-treated patients, and this difference was statistically significant (9% vs. 3%; odds ratio, 2.73; P<0.001) [14]. Hypercholesterolemia was prospectively studied in the BIG 1-98 trial. The results showed a significantly higher prevalence of hypercholesterolemia in patients treated with letrozole than in those treated with tamoxifen (50.6% vs. 24.6%, p <0.001). However, the majority of these cases of hypercholesterolemia were grades 1 and 2 [15]. In contrast, the MA.17 trial lipid substudy showed no significant changes in cholesterol levels induced by letrozole (16% vs. 16%, p=0.79) over a period of 3 years after 5 years of tamoxifen treatment [19]. The TEAM trial reported that the incidence of hypercholesterolemia at 12 months was significantly lower with tamoxifen than with exemestane (P=0.012) [16]. In contrast, in the IES trial, there was no difference in hypercholesterolemia levels between patients on exemestane and those treated with tamoxifen (7.2% versus 6.0%, p=0.12) [20]. In another study examining the lipid profiles of 55 postmenopausal women with early breast cancer who switched to exemestane after at least 2 years of tamoxifen, triglycerides and HDL-C cholesterol significantly decreased in the exemestane group, while LDL-C significantly increased at the end of 1 year study period. Comparative studies between AIs after 12 weeks of treatment with exemestane and anastrozole among early stage breast cancer patients showed no clinically significant impact on total cholesterol, HDL-C, LDL-C or triglycerides. However, anastrozole showed an increase in HDL-C, whereas exemestane showed a decrease in HDL-C levels [21]. At a median follow-up of 24 weeks, the LEAP trial, a phase I randomized clinical trial of 90 evaluable healthy volunteers receiving anastrozole, letrozole, or exemestane, showed no significant change in lipid parameters in women exposed to anastrozole, whereas letrozole induced a significant increase in triglyceride levels without affecting atherogenic ratios. Exposure to exemestane resulted in a significant increase in the atherogenic ratios of LDL-C/HDL-C and apolipoprotein B/apolipoprotein A1 compared to anastrazole and letrozole [22]. In the TEAM Japan sub-study of the National Surgical Adjuvant Study BC 04, significant differences were observed in the lipid profiles treated with exemestane, anastrozole, and tamoxifen. Compared with anastrozole, total cholesterol was significantly lower in exemestane patients at 3 months and 1 year (p=0.03 and 0.0076, respectively). HDL C was slightly decreased in exemestane patients and was significantly lower than that in anastrozole patients at 3 months and 1 year. (p=0.017 and 0.0013, respectively) [25]. A recent study in China also noted favorable changes in the lipid profile with the use of a steroidal AI, exemestane, compared with those treated with non-steroidal AIs, Anastrozole and Letrozole. The cumulative incidence of serum lipid events at 24 months in the steroidal and non-steroidal groups was 25.3% and 37.0% respectively. Time to lipid event analysis revealed that steroidal AIs were associated with a 36% lower incidence of lipid events, even when compared with non-steroidal AI, hazard ratio (HR), 0.64 [95% confidence interval (CI)] 0.44-0.93;p=018.) [18]. The long-term risk of atherosclerosis due to cancer treatment is becoming an important parameter in the era of improved survival among patients with early stage breast cancer. It remains uncertain whether AI use may account for the potential detrimental effects on atherosclerosis when used for a longer duration. To the best of our knowledge, this prospective study is the first randomized controlled trial designed to identify changes in the lipid profiles of Filipino postmenopausal women with hormone-sensitive breast cancer receiving adjuvant aromatase inhibitors.

Methodology

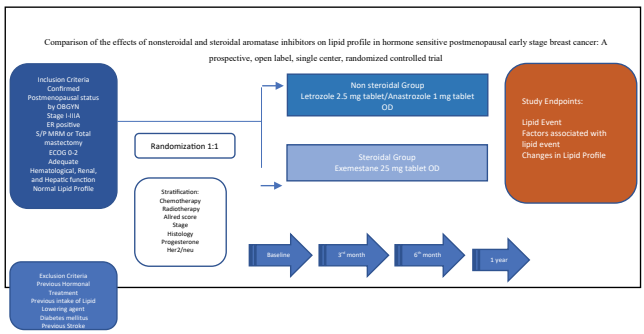
Study design: A prospective, single-center, open-label, randomized controlled study was conducted in the Veterans Memorial Medical Center Section of Medical Oncology to compare the changes in lipid profile in postmenopausal hormone-sensitive early stage breast cancer treated with either nonsteroidal AI (Letrozole 2.5 mg tablet/ Anastrozole 1 mg tablet once a day) or steroidal AI (Exemestane 25 mg

tablet once a day) for 1 year.

Patient and procedures: Post-menopausal women, as confirmed by obstetrics and gynecology specialist, who underwent modified radical mastectomy or total mastectomy for stage I, II, and IIIA estrogen-positive breast cancer; had an ECOG performance status of zero to two; had adequate hematological, renal, and hepatic function (defined as creatinine clearance by CKD-EPI >60 ml/min/1.73 m^2; aspartate aminotransferase or alanine aminotransferase <45 IU; hemoglobin >100 mg/L; Absolute Neutrophil count >2,000; platelet >150 x 10^9/L; had satisfied the lipid criteria (LDL-cholesterol (<160 mg/dL); and HBA1C of <7%; and had never been treated for a lipid metabolism disorder, were enrolled in this study. Eligible patients were randomized in to 1:1 using Randomizer application software version 2.0, to receive nonsteroidal AI (Letrozole 2.5 mg tablet/Anastrozole 1 mg tablet once a day) or steroidal AI (Exemestane 25 mg tablet once a day). Nonsteroidal and steroidal groups were stratified according to stage, chemotherapy, radiation therapy, lymph node status, histologic subtype, progesterone receptor, Her2/neu receptor, and Allred score. In the nonsteroidal AI group, an equal number of patients were allocated to receive either Letrozole or Anastrazole. Patients with a previous intake of endocrine therapy and lipid-lowering agents, obesity (BMI>25 kg/m^2), hypertension (>130 mm Hg/>80 mm Hg), diabetes mellitus, and stroke within the past 6 months were excluded from the study. The study recruitment was conducted between September 2020 and August 2021. Written consent was obtained from patients before enrollment. Prior to randomization, consultation with dietary services was conducted. A list of foods was provided to facilitate compliance with the recommended daily dietary fat reference intake for Filipinos. During the course of treatment, medication compliance was assessed using indirect methods of patient adherence such as refill prescriptions, pill counting, and assessment of clinical response. Only a 30-tablet prescription was dispensed monthly. A daily alarm was set up on the patient's phone. Each participant kept a diary of weekly intake with special attention paid to cholesterol-rich food. At each desired point of evaluation, patient adherence to prescribed daily fat intake was assessed through disclosure of weekly food diaries and eating patterns via telemedicine. Continuous counselling on information on dietary fiber, types of dietary fats and protein, reiteration of appropriate food choices, portion size control and measurement of daily dietary intake was rendered.

Telemedicine consultations were scheduled monthly to facilitate patient education, motivation, and support.

Conceptual framework



Endpoints: The primary endpoint of this study was the cumulative incidence of lipid events as defined by the 2015 Updated Clinical Practice Guideline for the management of dyslipidemia in the Philippines [23] and the Cooper Clinic Longitudinal Study [24] (high LDL-cholesterol (>160 mg/dL) during the 12 months of treatment, or initiation of lipid-lowering medication. Other study endpoints included factors associated with lipid event during the 12 month follow up and changes in the lipid profile during 12 months of treatment.

Sample collection, assessment time points, and measurement of lipid profiles

Physical examination and collection of laboratory samples were scheduled at baseline and, at 3, 6, and 12 months after initiation of aromatase inhibitors. Fasting (at least 12h) blood samples were collected for the estimation of serum lipid parameters, including total cholesterol (TC), LDL-C, HDL-C, and Triglycerides (TG), in the pathology section of the Veterans Memorial Medical Center. Patients with documented serum lipid event patient were sent for consultation at the Heart Institute, Veterans Memorial Medical Center for appropriate medical management.

Sample size: The cumulative incidence rates of serum lipid event at 12 months were derived from the data reported by Wang et al [18]. For the purpose of this research, 1 year proportions for sample size calculation were set to 0.18 for the steroidal group and to 0.26 for non-steroidal group based on the average expected proportion.

Statistical analysis: For numerical variables, the mean and standard deviation reported for each group and were compared using the Wilcoxon Rank-Sum Test. For categorical variables, frequency and proportion were reported for each group and compared using either the Chi-Square Test on Multiple Proportions or Fisher's exact test, whichever was applicable. Multivariate tests were performed to assess the equality of the two profiles by observing outcomes over time. First, the test of parallelism was used to check whether the profiles were parallel to each other or if the trend was similar for both profiles. Test of separation or group differences was performed if all means at different times were equal between the two profiles. Finally, test of flatness determined whether the two profiles were flat and whether the means were equal across time for both profiles. Kaplan-Meier curves were constructed to estimate survivor function against the occurrence of serum lipid event. A log-rank test was performed to evaluate whether there was a difference in survivor functions against lipid event occurrence across drug treatments and other factors associated with the outcome. All analyses were performed using STATA software for statistics and data science.

Results

The study recruited 34 patients between October 20, 2020 and August 31, 2021, at the Veterans Memorial Medical Center, with 18 patients randomly assigned to non-steroidal AI and 16 patients who received steroidal AI (exemestane). Of the 18 patients who received non-steroidal AI, 10 were treated with letrozole and 8 were treated with anastrozole. The treatment groups were well balanced (Table 1). All 34 patients completed lipid measurements at all time points.

The cumulative incidence of serum lipid event at 12 months in the non-steroidal and steroidal arms was 66.67% (40.32 – 85.55%) and 68.75% (40.16 – 87.82%), respectively (Figure 1).

The factors associated with serum lipid event were analyzed using univariate and multivariate analyses. In both analyses, LDL-C (HR-1.04, 95% CI 1.01-1.07; p-0.001) and TC (collinear with LDL-C) were significantly associated with serum lipid event (Table 2). There was no significant difference in serum lipid events between the treatment arms

Table 1. Baseline Comparison of Treatment Arms.

	Non-Steroidal (Letrozole/ Anastrozole) n = 18	Steroidal (Exemestane) n = 16	p-value
Age	60.61 ± 9.57	60.06 ± 6.17	0.691
Stage			
IA	0 (0.00%)	1 (6.25%)	
IB	2 (11.11%)	1 (6.25%)	
IIA	4 (22.22%)	3 (18.75%)	0.493
IIB	5 (27.78%)	8 (50.00%)	
IIIA	7 (38.89%)	3 (18.75%)	
Tumor Size			
T1	3 (16.67%)	2 (12.50%)	
T2	10 (55.56%)	10 (62.50%)	1.000
T3	5 (27.78%)	4 (25.00%)	
Nodal Status			
N0	5 (27.78%)	6 (37.50%)	
N1	10 (55.56%)	8 (50.00%)	0.898
N2	3 (16.67%)	2 (12.50%)	
ER	7.39 ± 0.78	7.63 ± 0.72	0.290
PR	6.11 ± 2.72	4.94 ± 3.96	0.867
HER2/neu			
0	12 (66.67%)	9 (56.25%)	
1+	4 (22.22%)	4 (25.00%)	0.888
2+	2 (11.11%)	3 (18.75%)	
Adjuvant Chemotherapy			
No	3 (16.67%)	2 (12.50%)	1.000
Yes	15 (83.33%)	14 (87.50%	
Anthracycline-based Chemo			
No	5 (33.33%)	3 (21.43%)	0.682
Yes	10 (66.67%)	11 (78.57%)	
Adjuvant Radiation Treatment			
No	5 (27.78%)	6 (37.50%)	0.545
Yes	13 (72.22%)	10 (62.50%)	
BMI			
Non-overweight	10 (55.56%)	11 (68.75%)	0.429
Overweight	8 (44.44%)	5 (31.25%)	

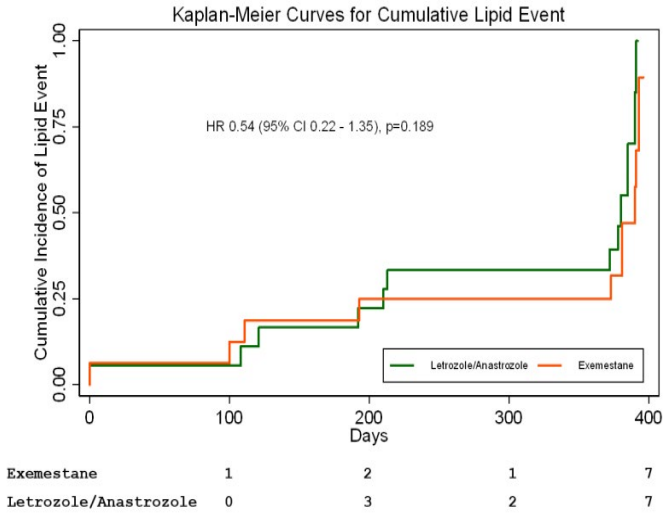


Figure 1. Kaplan–Meier curve for cumulative lipid events in patients with breast cancer treated with exemestane or letrozole/anastrozole.

Table 2. Multivariate survival analysis of factors associated with incidence of lipid-event.

Variables	Univariate		Multivariate	
	HR, 95% CI	p-value	HR, 95% CI	p-value
Exemestane (ref: Anastrozole/Letrozole)	0.54 (0.22, 1.35)	0.189 ns	0.69 (0.22, 2.17)	0.522 ns
Cholesterol	1.03 (1.01, 1.07)	0.003 *	Collinear with LDL	
Triglyceride	1.00 (0.98, 1.03)	0.758 ns	1.01 (0.98, 1.04)	0.578 ns
HDL	0.95 (0.89, 1.01)	0.109 ns	0.98 (0.92, 1.05)	0.534 ns
LDL	1.05 (1.02, 1.07)	0.001 *	1.04 (1.01, 1.07)	0.013 *
Age	1.02 (0.96, 1.08)	0.539 ns		
Stage (ref: IA)				
IB	6.76 (0.60, 75.78)	0.121 ns		
IIA	4.98 (0.48, 52.01)	0.180 ns		
IIB	2.41 (0.30, 19.43)	0.410 ns		
IIIA	1.99 (0.21, 18.60)	0.546 ns		
Tumor Size (ref: T1)				
T2	0.94 (0.33, 2.71)	0.909 ns		
T3	0.63 (0.19, 2.08)	0.445 ns		
Nodal Status (ref: N0)				
N1	1.02 (0.40, 2.62)	0.963 ns		
N2	1.08 (0.32, 3.71)	0.899 ns		
ER ALLRED Score	0.96 (0.50, 1.87)	0.914 ns		
PR ALLRED Score	1.07 (0.94, 1.22)	0.304 ns		
HER2/neu (ref: 0)				
1+	0.81 (0.29, 2.32)	0.700 ns		
2+	0.94 (0.32, 2.72)	0.906 ns		
Adjuvant Chemotherapy (ref: No)	1.39 (0.41, 4.74)	0.599 ns		
Anthracycline-based Chemo (ref: No)	0.34 (0.12, 1.00)	0.050 ns		
Adjuvant Radiation Treatment (ref: No)	0.76 (0.32, 1.82)	0.543 ns		
Overweight (ref: Non-overweight)	0.74 (0.31, 1.77)	0.499 ns		

(HR, 0.69; 95% 0.22-2.17; p-0.522).

Among the 34 records, the mean exit time was approximately 324.24 days (10.8 months) with a standard deviation of 102.42 days (median, 380 days). The earliest serum lipid event was 100 days (3.3 months) and the latest was 395 days (13.2 months). Among the 23 cases, the mean exit time was 296.35 days (9.9 months) with a standard deviation of 114.89 days (median, 374 days) (Table 2). The mean observed absolute values and corresponding SDs for each lipid parameter at baseline and at 3, 6, and 12 months after baseline are presented in (Table 3), while the mean observed changes from baseline values over the study period are presented in (Table 4). The increase in cholesterol and LDL and the decrease in HDL across months were statistically significant in both the Letrozole/Anastrozole and Exemestane groups. Meanwhile, only the changes at 6^{th} and 12^{th} months in triglycerides were significant from the baseline reading in the exemestane group.

When demographic factors were stratified into treatment groups (Table 5), PR was a significant factor for serum lipid event ($p = 0.022$). The point biserial correlation coefficient was 0.5686, signifying that there was a moderate positive association between PR and serum lipid event among those treated with exemestane.

Profile analyses were performed to assess equality between the two treatment groups (Figure 2). The TG, HDL, TC, and LDL levels at different time points in both treatment arms were equal and showed an equal trend.

Table 3. Observed values for lipid parameters across the study period (mean ± standard error).

	Cholesterol		HDL		LDL		Triglyceride	
	L/A	E	L/A	E	L/A	E	L/A	E
Baseline	172.9 ± 2.2	172.1 ± 3.0	55.4 ± 1.8	56.7 ± 1.9	90.7 ± 1.8	88.2 ± 2.1	134.2 ± 1.3	136.1 ± 1.4
3 months	191.8 ± 5.3	191.2 ± 5.4	41.9 ± 1.7	38.9 ± 2.4	123.7 ± 6.0	125.2 ± 6.2	131.3 ± 2.9	135.1 ± 2.9
6 months	198.7 ± 3.1	200.0 ± 4.6	31.9 ± 2.5	35.4 ± 2.0	140.1 ± 4.8	136.0 ± 5.4	133.4 ± 4.0	143.0 ± 2.2
12 months	221.3 ± 6.4	216.9 ± 4.7	34.2 ± 2.3	31.3 ± 1.8	159.9 ± 7.5	155.0 ± 5.1	135.9 ± 3.7	148.4 ± 3.6

Table 4. Observed changes from baseline values over the study period.

Change from baseline		3 months		6 months		12 months	
		Mean ± SE	p-value	Mean ± SE	p-value	Mean ± SE	p-value
Cholesterol	L/A	**18.9 ± 5.4**	0.0028 *	26.1 ± 3.2	<0.001 *	50.0 ± 6.5	<0.001 *
	E	**19.1 ± 5.1**	0.0020 *	27.9 ± 5.2	<0.001 *	45.1 ± 7.2	<0.001 *
HDL	L/A	**-13.5 ± 2.5**	<0.001 *	-23.9 ± 3.1	<0.001 *	-21.1 ± 3.7	<0.001 *
	E	**-17.8 ± 3.8**	<0.001 *	-20.6 ± 3.7	<0.001 *	-24.4 ± 3.8	<0.001 *
LDL	L/A	**33.0 ± 5.6**	<0.001 *	50.1 ± 4.3	<0.001 *	70.7 ± 7.9	<0.001 *
	E	**37.1 ± 6.3**	<0.001 *	47.02 ± 5.8	<0.001 *	66.8 ± 5.6	<0.001 *
Triglyceride	L/A	**-2.9 ± 3.0**	0.3501 ns	-0.7 ± 4.7	0.8794 ns	1.6 ± 3.4	0.6556 ns
	E	**-1.1 ± 2.8**	0.7106 ns	7.4 ± 2.6	0.0130 *	13.3 ± 3.2	0.0018 *

Table 5. Factors of Serum Lipid Event per Treatment Arm.

	Non-Steroidal (Letrozole/Anastrozole)		Steroidal (Exemestane)	
	p-value	Decision	p-value	Decision
Age	0.987	Not associated	0.892	Not associated
Stage	0.140	Not associated	1.000	Not associated
Tumor Size	0.636	Not associated	0.780	Not associated
Nodal Status	1.000	Not associated	0.333	Not associated
ER ALLRED Score	0.421	Not associated	0.126	Not associated
PR ALLRED Score	0.456	Not associated	0.022	Associated
HER2/neu	0.616	Not associated	0.621	Not associated
Adjuvant Chemotherapy	0.245	Not associated	1.000	Not associated
Anthracycline-based Chemo	0.560	Not associated	0.258	Not associated
Adjuvant Radiation Treatment	0.615	Not associated	0.588	Not associated
BMI	1.000	Not associated	1.000	Not associated

Table 6. Adverse events.

	Letrozole/Anastrozole (n=18)	Exemestane (n=16)
Arthralgia	7 (38%)	6 (37%)
Myalgia	7 (38%)	7 (43%)
Hot flushes	1 (5%)	2 (13%)
Vaginal dryness	2 (11%)	1 (6%)
Rash	1 (5%)	0
Headache	1 (5%)	2 (13%)
Dizziness	1 (5%)	1 (6%)

The mean TG levels (Figure 2A) at each time point were significantly different ($p < 0.01$). It can be observed from the profile plot that at baseline (time = 0), the means were close to each other but started to become more distant from the 3rd month (time = 3) up to the 12th month (time = 12). Throughout the monitoring period, the mean TG level of samples treated with exemestane was consistently higher than that of samples treated with Letrozole or Anastrozole.

(Figure: 2). (A) Triglyceride, (B) high-density lipoprotein cholesterol, (C) total cholesterol, (D) Low-density lipoprotein levels at different time points over the course of exemestane or anastrozole/letrozole treatment in women with early breast cancer.

The safety profiles in both treatment groups were consistent with the known side effects of individual AIs (Table: 6). The most common adverse events in both treatment groups were arthralgia, myalgia, and hot flushes. No adverse events of grade 3 or higher were reported. None of the patients discontinued treatment because of drug-related toxicity.

Discussion

The present analysis showed that adjuvant treatment with nonsteroidal and steroidal AIs at 1 year significantly altered the lipid profile of post-menopausal early breast cancer patients. Previous landmark studies on third-generation AIs have been restricted to identifying changes in total cholesterol levels. ATAC noted that anastrozole was associated with higher incidence of hypercholesterolemia than tamoxifen [14]. Comparing letrozole to tamoxifen, BIG 198 trial showed 43.6% of letrozole treated patients developed hypercholesterolemia [15]. While IES study did not systematically measure cholesterol levels, hypercholesterolemia was still reported to be 7.2% in the exemestane arm. Further profiling of lipid parameters is required [26]. As most of these data were obtained from studies comparing AI with tamoxifen, drawing conclusions regarding the benefits of AIs on lipid metabolism is difficult owing to the known protective lipid-lowering effects of tamoxifen [27]. Hence, comparative the studies of effects of aromatase inhibitors on lipid metabolism have been conducted.

The LEAP trial directly compared the safety parameters of exemestane, letrozole and anastrozole in 90 healthy post- menopausal women. The initial results showed that there was no significant difference between letrozole and anastrozole in their effects on LDL: HDL ratios, TG concentrations, and non-HDL concentrations. However, exemestane was associated with a decreased HDL: LDL ratio (p=0.047) compared with anastrozole. There was no median change from baseline in TC, a slight increase in anastrozole, or a non-significant decrease in exemestane levels [28].

In a head-to-head comparison of steroidal and nonsteroidal agents among Chinese women with early breast cancer, in which the cumulative incidence of lipid events was, to our knowledge, first used as a primary endpoint, exemestane was associated with a 36% lower incidence of lipid events when compared to non-steroidal AIs, with a hazard ratio of 0.64 [95% confidence interval, 0.44 to 0.33; p=0.018] [18]. This significantly favorable effect on the cumulative incidence of lipid events of exemestane was not confirmed in the present analysis, as

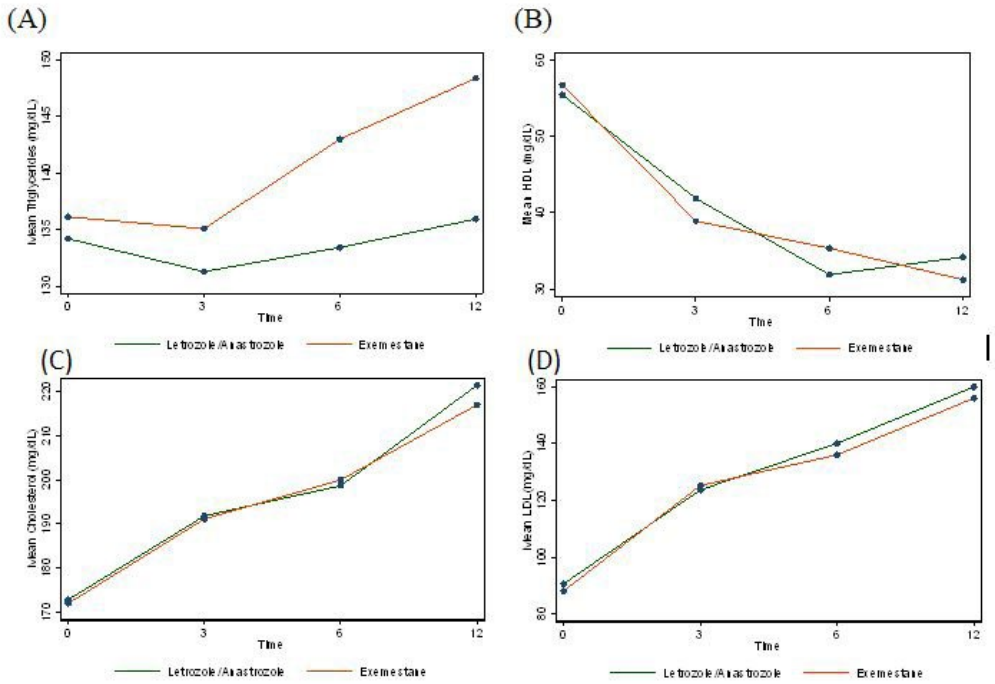


Figure 2. (A) Triglyceride, (B) high-density lipoprotein cholesterol, (C) total cholesterol, (D) Low-density lipoprotein levels at different time points over the course of exemestane or anastrozole/letrozole treatment in women with early breast cancer.

no significant difference was demonstrated (p=0.522).

Interestingly, the cumulative incidence of lipid events among Filipino post-menopausal early breast cancer patients was 66.67% and 68.75% in the letrozole/anastrozole and exemestane groups, respectively, at 12 months compared to the estimated 1 year incidence in the Chinese cohort, 26.46% in the letrozole/anastrozole group and 18.23% in the exemestane group [18]. In fact, the risk of serum lipid event was numerically higher by 2.08% among those treated with exemestane in the present analysis.

Racial and ethnic differences in the lipid metabolism have been explored in several studies. Of note, Filipino men (73%) and women (63%) had the highest prevalence rates of high LDL-C among Asian subgroups, non-Hispanic whites, non-Hispanic blacks, and Hispanics [33]. This may prove that there exists an inherent ethnicity-specific susceptibility and permit consideration as an independent factor of lipid metabolism.

Other findings are compatible with those of previous studies that showed significant changes in the lipid profile of nonsteroidal and steroidal AIs in early stage breast cancer. Hozumi et. Reported a compromised lipid profile with anastrozole among 38 post-menopausal Japanese women with early stage breast cancer. Anastrozole significantly increased serum TC (p=0.037), LDL (p=0.015), and HDL (p=0.013) after 3 months of treatment [29] with a significant increase in TC (p=0.05), LDL (p<0.01), and ApoB (p=0.05) in the serum, as well as in the atherogenic risk ratios TC: HDL ratio (p<0.005) observed after 16 weeks of Letrozole treatment [30]. Also, a significant increase in LDL (p<0.01) and a significant decrease in HDL (p<0.05) were observed after 1 year of treatment with exemestane [31]. In our study, significant differences compared to baseline were seen across time points in TC, LDL, and HDL.

In a randomized phase II study of 122 post-menopausal women, exemestane demonstrated favorable effect on TG over time, leading to a reduction that is statistically significant (p=0.002) at week 24 compared with baseline level [32]. Similarly, Wang et. al noted substantial decrease in TG after exemestane indicating a lowering effect of steroidal [18]. In this study, at 3rd month, a similar non-significant drop in TG levels was observed (p=0.7). However, at the 6th (p= 0.0130) and 12th months (0.0018), the beneficial effect of lipid stabilization of exemestane was eventually lost. To mitigate the effects of environmental factors such as unhealthy lifestyle and eating habits, a diary listing daily food intake, with reference to the Nutritional Guide Pyramid provided by dietary services, was obligatory. In this study, baseline body mass index had no effect on lipid events.

Asperger et. Investigated the involvement of progesterone receptors in cholesterol metabolism to identify new mechanisms by which progesterone receptors increase lipid metabolism. The progesterone receptor, specifically membrane component 1, interacts with key enzymes in the cholesterol synthesis pathway, alters protein expression, and results in increased lipid levels [34]. This association was confirmed in this study among those who received exemestane. As PR score increased, chance was high that there is a serum lipid event. However, more studies are needed to determine whether PR can be considered a negative predictive biomarker of lipid events in exemestane.

The cohort in this study at baseline had no indication to be initiated on lipid-lowering agents as per the 2015 Updated Clinical Practice Guideline for the management of dyslipidemia in the Philippines [23]. Extending further eligibility using the Cooper Clinic Longitudinal Study[24] reaffirmed that the present population in this study has a low 10 year estimated risk of atherosclerotic cardiovascular disease, a subset of the population where no delineated benefit of statin use was demonstrated [24]. This current health state remains a crucial phase since the introduction of AIs has significantly altered lipid

metabolism. Such a change, albeit generally small, might be sufficient to alter a patient's risk category and objectively qualify the patient for a lipid-lowering agent. In the adjuvant setting, monitoring of blood lipid parameters becomes an even more important active role of the clinician because patients are expected to be exposed for longer than in the metastatic setting.

In general, treatment with AI outweighs any of the disadvantages in lipid metabolism, especially in those with a high risk of recurrence [14-16]. However, if these agents are used in patients with low-risk early breast cancer, such as in our cohort; the impact of lipid profiles on treatment decisions remains a subject of discussion.

This study had several limitations: (1) Due to the restrictions imposed by COVID 19, the lipid profile in a central laboratory was not determined. However, the same Friedewald's formula for LDL was ascertained; (2) this study failed to recruit the pre-planned number of subjects due to delayed breast surgeries as a consequence of tight protocols during pandemic surges; (3) all patients analyzed were from a single center, decreasing the chances of applicability in the general Filipino population and worldwide; (4) with a short follow-up of 1 year, aromatase inhibitor-induced changes in lipid profile as surrogate markers of increased risk for major cardiovascular outcomes were not evaluated; (5) innovator and generic agents were used as study drugs. No comparative studies between innovator and biosimilar agents in terms of changes in lipid profile have been published to date, and (6) compliance with the recommended fat diet was limited only to weekly food diaries and self-confession of dietary habits.

In conclusion, in post-menopausal early breast cancer, treatment with either steroidal or non-steroidal AI showed no significant difference in cumulative lipid events at 1 year. More importantly, the present study added to the existing data bank that AI significantly alters mean TC, LDL, and HDL levels over time. Focused clinical trials studying these changes in lipid profile and their impact on cardiovascular morbidity should be pursued.

Acknowledgment

None

Conflict of Interest

None

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