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The balance between risks and benefits: Long-term use of aromatase inhibitors

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ABSTRACT

The third-generation aromatase inhibitors (AIs) are gradually displacing tamoxifen as the preferred adjuvant endocrine treatment for hormone-receptor-positive early breast cancer in postmenopausal women, having demonstrated superior efficacy in clinical trials. However, for the AIs to gain widespread acceptance in the adjuvant setting, good long-term tolerability must also be demonstrated, particularly as many women with early breast cancer can now expect to live for over a decade after initial diagnosis. Tamoxifen has been widely used in this setting for over 30 years, and the side effects associated with its long-term use are well documented. Many adverse events that occur with tamoxifen are predictable consequences of its antiestrogenic actions, including hot flushes and mood disturbances. However, tamoxifen also has estrogenic properties in some tissues, which are associated with desirable and undesirable effects. Of particular importance, tamoxifen can cause unwanted gynecological events, including an increased risk of developing endometrial cancer, and thromboembolic disease. Conversely, tamoxifen protects against postmenopausal bone loss, modestly lowers cholesterol levels and may protect against cardiac disease.

As the number of women treated with AIs increases, long-term safety data relating to these agents will gradually accumulate. Safety data are currently available from early adjuvant trials comparing an AI with tamoxifen during the first 5 years after surgery (sequential and substitution strategies), and from the extended adjuvant setting, comparing letrozole with placebo after completion of 5 years of tamoxifen therapy (the MA.17 trial). In early adjuvant studies, the use of tamoxifen as a comparator can complicate the analysis of safety data, particularly in tissues where tamoxifen has beneficial, estrogenic effects.

Studies in the early adjuvant setting have shown that AIs are generally well tolerated and are associated with a lower incidence of vaginal bleeding, thromboembolic disease and endometrial cancer than tamoxifen. Results from these studies have suggested that AIs are associated with musculoskeletal side effects, including bone loss, osteoporosis and fractures, cardiovascular disease and hypercholesterolemia. However, analysis of safety data from MA.17, with a placebo control, showed no evidence of adverse effects of letrozole on the cardiovascular system or lipid profiles. When the data from early and extended adjuvant studies are considered together, it can be concluded that the increased incidences of hypercholesterolemia and cardiovascular disease seen in patients taking an AI probably reflect the lack of the protective effects of tamoxifen in these patients rather than a detrimental effect of the AI.

Bone loss is a predictable consequence of the near-complete elimination of circulating estrogen achieved by third-generation AIs in postmenopausal women. In the MA.17 trial, although more women on letrozole reported new, self-diagnosed osteoporosis than those

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on placebo, the number of clinical fractures did not differ significantly between the two treatment arms, however, further follow-up is needed. Furthermore, ongoing studies are evaluating the role of bisphosphonates and other agents to better characterize and potentially ameliorate AI-associated bone loss in postmenopausal women.

The adverse events associated with AI use are predictable and manageable. On the basis of current data, the tolerability of AIs in the adjuvant setting appears as good as that of tamoxifen, and some serious adverse events associated with tamoxifen use are avoided. Further studies and longer follow-up from current trials will help to determine in more detail the long-term effects of this class of drugs.

1. Introduction

The third-generation aromatase inhibitors (AIs) are gradually displacing tamoxifen as the first choice of adjuvant endocrine therapy for hormone-receptor-positive (HR+) early breast cancer, having demonstrated superior efficacy in large, randomized, clinical trials. As the results from these trials become more widely disseminated, and the number of women taking AIs increases, the accumulating data will help physicians to understand the risks and benefits associated with AI use. Both efficacy and good long-term safety data are essential to achieving widespread acceptance of AIs in the adjuvant treatment of early breast cancer.

Large, randomized, controlled trials have shown that the safety profile of AIs is fairly predictable, and consistent with the known effects of estrogen deprivation. AIs and tamoxifen have some adverse events in common; for example, both AIs and tamoxifen are associated with classic symptoms of estrogen deprivation, such as hot flushes, sweating and mood disturbances. However, several adverse events have been attributed to only one or other agent. The estrogen agonist effects of tamoxifen in some tissues, including bone, the urinogenital tract and the cardiovascular system, result in tamoxifen-specific effects that can be detrimental or beneficial. These estrogenic effects complicate interpretation of safety data from studies where tamoxifen is the comparator: rather than acting as a neutral placebo-type control, tamoxifen has some active effects in the opposite direction to those of AIs, which induce near-complete estrogen deprivation. Determining the actual effects of AIs on tissues in which tamoxifen has beneficial effects can, therefore, be difficult.

Studies comparing AIs with tamoxifen in the early adjuvant setting have indicated that AIs may have detrimental effects on the musculoskeletal and cardiovascular systems, and lipid metabolism when compared with tamoxifen.[1–5] However, of these adverse events, only increased musculoskeletal effects were associated with AI therapy in the MA.17 trial.[6] Among the musculoskeletal effects, loss of bone mass (a known side effect of estrogen deprivation) is probably the most clinically significant. In light of the association between AI therapy and bone loss, studies are ongoing to determine how this predictable side effect can be managed.

AIs are proving to be more effective adjuvant therapies than tamoxifen, and current safety data suggest that they are also associated with fewer problematic side effects, including thromboembolic and gynecological events.[1–5] Findings from the MA.17 study comparing letrozole with placebo do not suggest that AIs have detrimental effects on lipid metabolism or the cardiovascular system.[6] Recent studies suggest that AI-associated bone loss can be managed with close follow-up and, probably, bisphosphonates or other antiresorptive agents. Hence, in addition to improved efficacy over tamoxifen, adverse events associated with AI use are both predictable and manageable, supporting the preferential use of AIs as adjuvant therapy in the majority of patients with HR+ disease. Through further research and improved understanding of the risks and benefits associated with AI therapy, it will be possible to maximize the clinical impact of AIs in the treatment of patients with HR+ early breast cancer.

2. Safety profile of AIs in the adjuvant setting

Adverse events associated with AI therapy have been reported in trials in the early and extended adjuvant settings. In the early adjuvant trials,[1–5] tolerability has been assessed in both sequential (AI after 2–3 years of tamoxifen) and substitution (upfront therapy immediately after surgery) treatment strategies. However, adverse events were not reported uniformly across trials and not all toxicity data were collected systematically. Differences in the adverse event profiles of the individual AIs may be expected, for example, between the steroidal (exemestane) and non-steroidal (anastrozole, letrozole) AIs; however, to date no detectable clinical differences have been demonstrated.

When assessing the side effects associated with an AI in early adjuvant trials, the estrogenic effects of tamoxifen in some tissues must be considered: the safety data from these trials represent the net difference between the effects of the AI and the effects of tamoxifen. Thus, some side effects seen in patients taking an AI may reflect the absence of a protective effect of tamoxifen rather than a detrimental effect of an AI. In support of this argument, some side effects that were associated with AI use in the early adjuvant setting were not associated with letrozole use in the extended adjuvant setting in the MA.17 study (Table 1).[6]

2.1. *Hot flushes*

Hot flushes, a classic symptom of estrogen deprivation, were reported in approximately 40% of women across all AI early adjuvant trials. No difference was seen in the incidence of hot flushes in women who switched from tamoxifen to

Table 1 – Safety profile of extended adjuvant letrozole therapy compared with placebo in the MA.17 trial

Adverse event	Letrozole (n = 2572)		Placebo (n = 2577)		p value
	Number	%	Number	%	
Hot flushes	1486	58	1383	54	0.003
Arthritis	167	6	137	5	0.07
Arthralgia	651	25	532	21	<0.001
Myalgia	380	15	310	12	0.004
Vaginal bleeding	145	6	196	8	0.005[a]
Hypercholesterolemia	418	16	411	16	0.79
Cardiovascular disease	149	5.8	144	5.6	0.76
New osteoporosis[b]	209	8.1	155	6.0	0.003
Clinical fracture	137	5.3	119	4.6	0.25
Discontinuations due to AEs	NR	4.9	NR	3.6	0.019

NR, not reported; AEs, adverse events.
a In favor of letrozole.
b Patient-reported.

exemestane compared with continued tamoxifen therapy (42% and 39.6%, respectively, $p = 0.28$) in the Intergroup Exemestane Study (IES).[1] Similar results were reported for patients switching to anastrozole (48%) compared with those staying on tamoxifen (50%, $p = 0.3209$) in the Austrian Breast & Colorectal Cancer Study Group (ABCSG)-8 trial, in which hot flushes were a predefined adverse event.[2] In contrast, fewer patients who received an AI upfront reported hot flushes than those who received upfront tamoxifen. Hot flushes were reported by 35.7% and 40.9% of women receiving anastrozole and tamoxifen, respectively, ($p < 0.0001$) in the Anastrozole, Tamoxifen Alone or in Combination study (ATAC),[3] and by 33.5% and 38% of women on letrozole and tamoxifen, respectively, in the Breast International Group (BIG) 1-98 trial.[4] In the MA.17 extended adjuvant trial, significantly more women on letrozole (58%) than on placebo (54%, $p = 0.003$) experienced hot flushes.[6]

2.2. *Gynecological symptoms*

Tamoxifen has estrogenic effects on the uterus, and is associated with an increased risk of developing invasive endometrial cancer. Gynecological symptoms, including vaginal bleeding and vaginal discharge, were significantly lower in patients receiving an AI than in those receiving tamoxifen in early adjuvant trials (Table 2).[1,3,4] Furthermore, vaginal bleeding was less common in patients receiving letrozole than in those taking placebo in the extended adjuvant setting, occurring in 6% and 8% of patients, respectively ($p = 0.005$).[6] Notably, across AI trials, endometrial cancer, a rare but well-documented side effect of tamoxifen therapy, was lower in women on an AI than on tamoxifen. Owing to the association between tamoxifen and invasive endometrial cancer, many women on tamoxifen undergo endometrial biopsies. The reduced requirement for such investigational procedures in women on an AI, as demonstrated in BIG 1-98 (2.3% vs 9.1% [$p < 0.001$] of women on letrozole and tamoxifen, respectively, required endometrial biopsies) and other trials (Table 2), could save many patients from unnecessary anxiety, and also considerably reduce healthcare costs associated with adjuvant therapy.

2.3. *Effect of AIs on lipid metabolism*

Data from early adjuvant studies comparing AIs with tamoxifen have suggested that AIs may have a detrimental effect on

Table 2 – Reduced incidence of gynecological symptoms and endometrial cancer with AIs in early and extended adjuvant trials

Trial	Treatment protocol	Event	AI (%)	Comparator (%)	p value
ATAC	Ana vs Tam	Vaginal discharge	3.5	13.2	<0.0001
		Vaginal bleeding	5.4	10.2	<0.0001
		Endometrial cancer	0.2	0.8	0.02
BIG 1-98	Let vs Tam	Vaginal bleeding	3.3	6.6	<0.001
		Endometrial biopsies	2.3	9.1	<0.001
		Endometrial cancer	0.1	0.3	0.18
IES	Tam → Exe vs Tam	Vaginal bleeding	4.0	5.5	0.05
		Gynecological symptoms	5.8	9.0	<0.001
		Endometrial cancer	0.21	0.46	NR
ABCSG/ARNO	Tam → Ana vs Tam	Vaginal bleeding/discharge	18	17	0.93
MA.17	Let vs Placebo	Vaginal bleeding	6	8	0.005

NR, not reported; Ana, anastrozole; Tam, tamoxifen; Let, letrozole; Exe, exemestane.

serum lipid profiles. In the trials of sequential therapy in the early adjuvant setting, disorders of lipid metabolism were more common in patients who switched to anastrozole after 2 years of tamoxifen than in those who remained on tamoxifen in the Italian Tamoxifen Arimidex (ITA) study, occurring in 9.3% and 4.0% of patients on anastrozole and tamoxifen, respectively ($p = 0.04$).[5] Serum lipids were not assessed in the IES and ABCSG/Arimidex–Novaldex (ARNO) trials.

Data from trials comparing AIs and tamoxifen upfront in the early adjuvant setting have also suggested that AIs may be associated with changes in serum lipid profiles. In the ATAC trial, hypercholesterolemia was more common in patients on anastrozole than tamoxifen (9% and 3.5%, respectively), but lipid data were not collected systematically, and a formal statistical analysis of these numbers has not been reported to date.[7] Upfront letrozole therapy was also associated with an increased incidence of hypercholesterolemia compared with upfront tamoxifen treatment (43.5% and 19.1%, respectively) in the BIG 1-98 study.[4] Over 80% of these events were grade 1 in both the letrozole- and tamoxifen-treated arms (35.1% and 17.3%, respectively) and, therefore, did not require any intervention. It should be noted that 90% of these measurements were made in non-fasting individuals, at variable times of day, and were not sent for centralized laboratory assessment. Furthermore, a single cholesterol measurement above the upper limit of normal at any scheduled 6-monthly visit was sufficient for a patient to be classified as hypercholesterolemic, and an adverse event to be recorded. Analysis of total serum cholesterol levels over a 60-month period in patients participating in BIG 1-98 showed that serum cholesterol remained constant in the letrozole arm and decreased by approximately 12% in the tamoxifen arm during the first 6 months: after 6 months, levels remained constant in both groups (Fig. 1).[4] It can be assumed that the changes in serum cholesterol levels observed in the first 6 months reflect the loss of the lipid-lowering effects of tamoxifen. The lipid-lowering properties of tamoxifen observed in this analysis are consistent with published data regarding the effect of selective estrogen receptor modulators on lipid metabolism.[8] In a comprehensive review of 10 trials of tamoxifen in postmenopausal women (6 of which compared tamoxifen with placebo), tamoxifen was shown to reduce lipid levels in all studies, with a median reduction of 12.5% (range 3–17). The change in total serum cholesterol was due to a reduction in low-density lipoprotein (LDL)-cholesterol, an important indicator of cardiovascular health. Tamoxifen was also shown to reduce total and, LDL-cholesterol, lipoprotein (a) and apolipoprotein B within 3 months of starting adjuvant therapy in a longitudinal study of patients with HR+ early breast cancer.[9] Preclinical studies have identified at least two mechanisms through which tamoxifen is thought to reduce plasma cholesterol levels and, hence, protect against cardiac disease.[10] These data suggest that the increased incidence of hypercholesterolemia seen in patients on an AI in the ATAC and BIG 1-98 studies may, in fact, reflect the lack of a beneficial effect of tamoxifen on lipid metabolism in these patients, which is not seen in patients taking an AI.

Data from the MA.17 trial comparing letrozole with placebo after 5 years of tamoxifen treatment also suggest that the absence of tamoxifen can explain the apparent effect of AIs on serum lipids in early adjuvant trials: there was no difference between the incidence of hypercholesterolemia in the two treatment arms in this trial (letrozole, 16%; placebo, 16%; $p = 0.79$).[6] In the lipid substudy of MA.17, MA.17L, serum lipid profiles were assessed at baseline and at 6, 12, 24 and 36 months in 347 non-hyperlipidemic patients enrolled in the trial. An increase in lipid parameters was seen within 6 months of finishing tamoxifen therapy in both treatment arms, consistent with the loss of tamoxifen's beneficial effect. No significant differences in cholesterol (total, LDL, high-density lipoprotein [HDL] and HDL/LDL ratio), triglycerides or lipoprotein a levels were seen between the two treatment arms, except for a marginal change in HDL-cholesterol at 6 months ($p = 0.049$), LDL-cholesterol at 12 months ($p = 0.033$) (Table 3) and triglycerides at 24 months ($p = 0.036$), suggesting

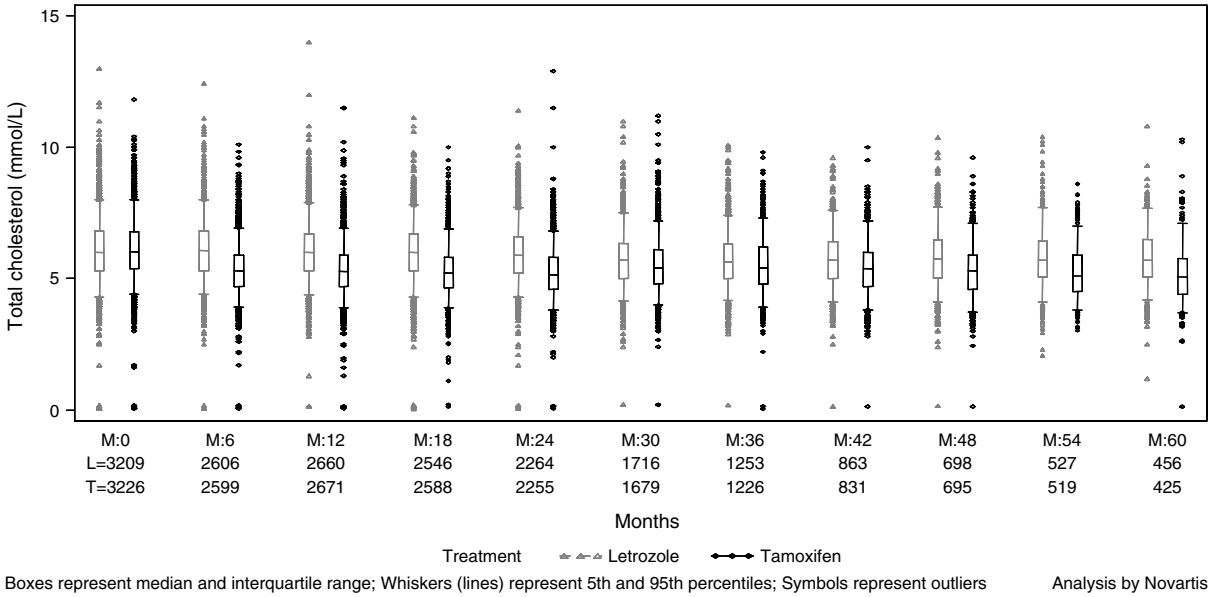

Fig. 1 – Effect of letrozole and tamoxifen on serum cholesterol.

Table 3 – Effect of extended adjuvant letrozole therapy on serum cholesterol levels, compared with placebo, in the lipid substudy of MA.17 (MA.17L)

Serum cholesterol	Treatment duration (months)	% change from baseline, mean (SD)		*p* value
		Letrozole	Placebo	
Total	6	13.58 (12.51)	12.49 (14.06)	0.32
	12	14.55 (14.95)	11.15 (15.57)	0.078
	24	13.35 (14.7)	10.19 (18.37)	0.34
	36	10.53 (16.39)	8.36 (24.5)	0.58
HDL	6	1.46 (15.47)	4.31 (13.41)	0.049
	12	3.07 (16.41)	3.21 (17.01)	0.91
	24	1.22 (18.7)	6.53 (29.54)	0.31
	36	2.08 (23.43)	12.9 (43.02)	0.33
LDL	6	25.4 (23.65)	23.4 (25.13)	0.48
	12	27.65 (27.35)	21.49 (29.82)	0.033
	24	23.07 (27.39)	22.03 (32.94)	0.89
	36	20.72 (25.98)	18.19 (43.56)	0.39

that letrozole does not significantly alter serum lipid parameters.[11] Furthermore, in studies in healthy postmenopausal women, no changes were seen in serum total, LDL- or HDL-cholesterol during 3 or 6 months of letrozole therapy.[12,13] Similarly, 2 years of exemestane therapy had no major effects on lipid profiles in postmenopausal women with early breast cancer compared with placebo.[14]

2.4. *Cardiac disease*

There is considerable debate concerning how AIs affect the cardiovascular system, and further investigation is required. The incidence of cardiovascular disease (CVD) was generally low in adjuvant AI trials. In all early adjuvant trials, the incidence of CVD was lower in patients on tamoxifen than in patients on an AI (Table 4). In the ATAC trial, a non-significant increase in the incidence of ischemic CVD was associated with anastrozole use (4.1% vs 3.4%, $p = 0.1$).[3] The overall incidences of grade 3–5 cardiovascular events were similar in patients on letrozole and tamoxifen (3.7% vs 4.2%). Similar incidences of cardiac events (of any grade) were also reported in patients on letrozole (4.1%) and tamoxifen (3.8%) in the BIG 1-98 trial, but the incidence of grade 3–5 cardiac events was higher in patients receiving letrozole than in those taking tamoxifen (2.1% and 1.1%, respectively, $p = 0.0003$), as was the incidence of cardiac failure (0.8% vs 0.4%, respectively, $p = 0.01$), although these events were uncommon in both treatment arms.[4] Non-significant increases in the incidence of CVD, excluding myocardial infarction but including cardiovascular events of limited clinical importance, such as hypertension (42.6% vs 39.2%, $p = 0.11$), and the incidence of myocardial infarction (0.9% vs 0.4%, *p* value not indicated), were reported in patients who switched to exemestane compared with those remaining on tamoxifen in the IES.

Table 4 – Cardiovascular and thromboembolic (TE) adverse events in adjuvant AI trials

Event	Trial	AI	Comparator	AI vs comparator (%)	*p* value
Ischemic CVD	ATAC	Ana	Tam	4.1 vs 3.4	0.1
CVD (excluding MI)	IES	Exe	Tam	42.6 vs 39.2	0.11
	MA.17	Let	Placebo	5.8 vs 5.6	0.76
Cardiac (any grade)	BIG 1-98	Let	Tam	4.1 vs 3.8	0.61
Cardiac (grade 3–5)				2.1 vs 1.1	<0.001
MI	IES	Exe	Tam	1.0 vs 0.4	NR
	ABCSG/ARNO	Ana	Tam	<1 vs <1	1.0
	MA.17	Let	Placebo	0.3 vs 0.4	NR
Venous TE	ATAC	Ana	Tam	2.8 vs 4.5	0.0004
Deep venous TE	ATAC	Ana	Tam	1.6 vs 2.4	0.02
Thromboembolic	BIG 1-98	Let	Tam	1.5 vs 3.5	<0.001
	IES	Exe	Tam	1.0 vs 1.9	0.003
	MA.17	Let	Placebo	0.4 vs 0.2	NR
Thromboses	ABCSG/ARNO	Ana	Tam	<1 vs <1	0.034
Embolism				<1 vs <1	0.064

Median follow-up: ATAC, 68 months; BIG 1-98, 25.8 months; IES, 30.6 months; ABCSG/ARNO, 28 months; MA.17, 30 months.
MI, myocardial infarction; NR, not reported; Ana, anastrozole; Tam, tamoxifen; Let, letrozole; Exe, exemestane.

Cardiac deaths were also slightly higher in patients who switched to exemestane than those who continued with tamoxifen in the IES (10 vs 8, respectively, p value not reported).[1] No difference in the incidence of myocardial infarction was reported between the two arms in the ABCSG/ARNO analysis.[2]

In contrast to data from the early adjuvant trials, there was no evidence of an increased incidence of CVD in patients receiving extended adjuvant letrozole therapy compared with patients taking placebo. CVD was recorded in 5.8% and 5.6% of patients on letrozole and placebo, respectively ($p = 0.76$; Fig. 2), and myocardial infarction was recorded in 0.3% and 0.4% of patients, respectively, suggesting that letrozole therapy is not associated with an increase in CVD.[6]

Data from adjuvant AI studies suggest that a trend for an increased incidence of cardiovascular events was evident when comparing an AI with tamoxifen, but not when comparing letrozole with placebo. These observations could be explained by beneficial effects of tamoxifen on cardiac tissue, which would be seen in the comparator group in early, but not extended, adjuvant trials. A cardioprotective effect of tamoxifen has been demonstrated in a meta-analysis of 32 trials, involving over 52,000 women, and comparing tamoxifen with a control group. This meta-analysis revealed a trend for a lower incidence of myocardial infarction, and significantly fewer deaths from myocardial infarction in women receiving tamoxifen compared with the control groups,[15] suggesting that tamoxifen may protect against heart disease. In accordance with the most recent American Society of Clinical Oncology (ASCO) technical assessment, which concluded that available data are insufficient to determine fully the effects of AIs on the cardiovascular system,[16] further investigation of this area, including whether all AIs are equivalent, is required. However, the available data suggest that the increased incidences of cardiac events in patients receiving early adjuvant AI therapy compared with those receiving tamoxifen, reflect the lack of a cardioprotective effect of tamoxifen in patients taking an AI. Data from the extended adjuvant setting, comparing letrozole with placebo, indicate that AIs do not have detrimental effects on the cardiovascular system.

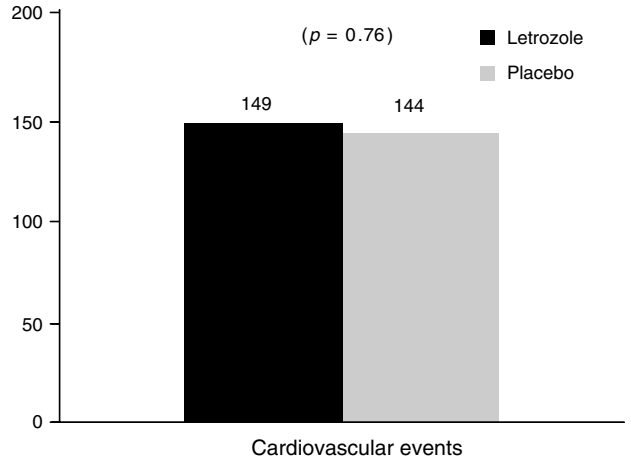

Fig. 2 – Cardiovascular events in patients receiving extended adjuvant letrozole therapy or placebo in the MA.17 trial.

2.5. *Thromboembolic disease*

Thromboembolic disease is a well-documented side effect of tamoxifen therapy that can cause considerable morbidity and mortality. Fewer thromboembolic adverse events were reported in patients taking an AI than in those taking tamoxifen in sequential and substitution early adjuvant studies (Table 4). Venous (2.8% vs 4.5%, $p = 0.0004$) and deep venous (1.6% vs 2.4%, $p = 0.02$) thromboembolic events were significantly less common in patients taking anastrozole upfront than in those taking tamoxifen in the ATAC trial.[3] Similarly, thromboembolic events of all grades (1.5% vs 3.5%, $p < 0.001$), and of grade 3–5 (0.8% vs 2.1%, $p < 0.0001$), occurred significantly less frequently in patients taking upfront letrozole than in those receiving tamoxifen therapy in the BIG 1-98 trial,[4] demonstrating a highly significant reduction in the incidence of thromboembolic disease.

Switching to exemestane after 2–3 years of tamoxifen therapy was also associated with a significant reduction in the incidence of thromboembolic disease, with 1.0% of patients on exemestane and 1.9% of patients on tamoxifen ($p = 0.003$) experiencing thromboembolic adverse events.[1] The incidence of serious thromboembolic adverse events was also significantly lower in patients receiving exemestane than in those taking tamoxifen (1.3% and 2.0%, respectively; $p = 0.007$).[1] The number of patients experiencing thromboses was also lower in patients on anastrozole than in those on tamoxifen, and there was a trend towards a reduction in the incidence of embolisms in patients on anastrozole in the ABCSG/ARNO analysis, although the incidence of these adverse events was below 1% in both treatment arms.[2]

The incidence of thromboembolic disease was very low in both arms of the MA.17 trial (0.4% and 0.2% in the letrozole and placebo arms, respectively),[6] indicating that letrozole is not associated with an increased risk of thromboembolic disease in this setting.

The lower incidence of thromboembolic disease seen with AIs compared with tamoxifen provides a further benefit to the patient, in addition to the reduced risk of breast cancer recurrence that is associated with AI treatment.

2.6. *Musculoskeletal adverse events*

Reports from early adjuvant trials indicate that musculoskeletal adverse events are more common in women taking an AI than in those on tamoxifen. Arthralgia and/or myalgia were more common in patients on an AI across early adjuvant trials,[1–4] and were also more common in patients receiving letrozole than in those taking placebo in the extended adjuvant setting.[6]

AI therapy was also associated with bone loss in all adjuvant trials, irrespective of the treatment strategy (Table 5). Loss of bone mass is a predictable side effect of the near-complete estrogen deprivation achieved by third-generation AIs. However, postmenopausal women are inherently at increased risk of osteoporosis resulting from the natural reduction in estrogen levels associated with menopause, and women with breast cancer are at greater risk of osteoporosis and fractures than age-matched controls, suggesting an intrinsic link

Table 5 – Osteoporosis and fractures in trials of AIs as early and extended adjuvant therapy

Trial	Treatment protocol	Adverse event	AI vs comparator (number of events)	AI vs comparator (%)	*p* value
ATAC	Ana vs Tam	Fractures	340 vs 237	11 vs 7.7	<0.0001
BIG 1-98	Let vs Tam	Fractures	225 vs 159	5.7 vs 4.0	<0.001
IES	Tam → Exe vs Tam	Osteoporosis	171 vs 134	7.4 vs 5.7	0.05
		Patients with fracture	72 vs 53	3.1 vs 2.3	0.08
ABCSG/ARNO	Tam → Ana vs Tam	Fractures	34 vs 16	2 vs 1	0.015
MA.17	Let vs Placebo	New osteoporosis[a]	209 vs 155	8.1 vs 6.0	0.003
		Clinical fractures	137 vs 119	5.3 vs 4.6	0.25

NR, not reported; Ana, anastrozole; Tam, tamoxifen; Let, letrozole; Exe, exemestane.
a Patient-reported.

between breast cancer and bone loss. These observations reinforce the importance of monitoring bone health in women receiving AIs.

Bone loss was seen in patients taking AIs in all early adjuvant studies, suggesting that exposure to tamoxifen for 2–3 years prior to AI therapy does not protect against AI-associated bone loss. Fractures were more common in patients receiving upfront anastrozole than tamoxifen ($p < 0.0001$) in the ATAC trial: 340 (11.0%) and 237 (7.7%) patients on anastrozole and tamoxifen, respectively, experienced a fracture.[3] Upfront letrozole was also associated with a higher incidence of fractures than tamoxifen in the BIG 1-98 trial, with 5.7% and 4.0% of patients, respectively, reporting a clinical fracture (*p* value not reported).[4] Similar results were seen in patients who switched to an AI in trials of sequential therapy. In IES, the incidence of osteoporosis was significantly higher in patients who switched to exemestane than in those who stayed on tamoxifen (7.4% and 5.7%, respectively, $p = 0.05$), and a trend was reported for more fractures in the exemestane group (exemestane, 3.1%; tamoxifen, 2.3%; $p = 0.08$).[1] In the ABCSG/ARNO trial, significantly more patients switching to anastrozole ($n = 34$, 2%) reported fractures than those remaining on tamoxifen (16 [1%] vs 34 [2%]; $p = 0.015$).[2] On the other hand, tamoxifen is known to have a protective, estrogenic effect on bone.[17]

Data from the placebo-controlled MA.17 extended adjuvant study also suggest that some bone loss occurs with AI use.[6] New, self-diagnosed osteoporosis was more common in patients receiving letrozole than in those receiving placebo, being reported in 209 (8.1%) and 155 (6.0%) patients, respectively ($p = 0.003$). A small increase in the incidence of clinical fractures was also seen in patients on letrozole (5.3% vs 4.6%), but this did not reach statistical significance ($p = 0.25$), suggesting that letrozole therapy did not increase fracture risk although based on short term follow-up.[6] The effect of extended adjuvant letrozole therapy on bone was investigated in more detail in the MA.17B bone substudy. Objective monitoring of bone mineral density (BMD) using dual-energy X-ray absorptiometry identified lower rates of newly diagnosed osteoporosis in both study arms, with no significant difference between the two treatment groups (letrozole 3%; placebo 0%; *p* value not significant).[18]

In light of these findings, the updated ASCO guidelines recommend an initial assessment of BMD in all postmenopausal women with breast cancer receiving AIs, with this examination repeated annually.[19]

2.7. *Management of AI-induced bone loss*

Effective management of the side effects associated with AI use, including bone loss, is important for optimal care. AI-associated bone loss could cause considerable morbidity and may, therefore, represent a barrier to the widespread acceptance of AIs as adjuvant therapy for HR+ breast cancer. Although hormone-replacement therapy, one of the older, standard treatments for postmenopausal osteoporosis, is contraindicated in women with HR+ breast cancer, recent clinical trials have shown that short-term AI-associated bone loss is manageable by monitoring and, where necessary, treatment with bisphosphonates. Longer follow-up and evaluation of the potential best timing for the introduction of a bisphosphonate or other anti-resorptive agent are ongoing. It is recommended that, if annual BMD measurements reveal a change in T-score >-1, patients should be provided with reassurance and lifestyle changes that could slow or prevent further bone loss. Calcium and vitamin D supplements should be initiated when changes in T-score are between -1 and -2.5. In patients experiencing considerable bone loss (T-score < -2.5), bisphosphonate therapy is recommended.[19]

Bisphosphonates bind to bone at sites of active metabolism, and potently inhibit bone resorption. Early, oral bisphosphonates were administered on a daily basis, and were associated with gastrointestinal toxicity. The newer bisphosphonate, zoledronic acid, is many times more potent than the first-generation compounds and is administered as a 15-min IV infusion at 6-monthly intervals, and does not cause gastrointestinal side effects.

The ability of zoledronic acid to prevent and/or treat AI-induced bone loss is currently being studied in the Z-FAST/ZO-FAST trials. Postmenopausal women receiving adjuvant letrozole therapy have been randomized to receive either upfront or delayed zoledronic acid, with treatment initiated in the delayed group when post-baseline BMD T-score decreased by at least -1 SD, or a fracture had occurred. Early results from the Z-FAST trial (based on 343 of 602 patients) revealed that zoledronic acid can prevent short-term AI-induced bone loss. Upfront zoledronic acid resulted in a mean increase in lumbar BMD of 2.02% compared with a mean reduction of 2.61% with

delayed treatment, after 1 year of treatment, resulting in a significant difference of 4.63% between the two treatment groups ($p < 0.001$).[20] Of the patients assigned to receive delayed zoledronic acid, only 8% met the criteria required to initiate zoledronic acid at 1 year of follow-up. Accrual has also recently been completed in the North Central Cancer Treatment Group (NCCTG) N03CC trial. Postmenopausal women who had received tamoxifen and were eligible for an AI have been enrolled and randomized to receive letrozole, calcium and vitamin D with either zoledronic acid upfront or when BMD has decreased >−2.0 SD.

Zoledronic acid was also shown to prevent treatment-induced bone loss in the ABCSG-12 trial of premenopausal women with breast cancer receiving goserelin plus either tamoxifen or anastrozole with or without zoledronic acid. In the absence of zoledronic acid, endocrine therapy was associated with significant bone loss, which occurred to a greater extent in women receiving anastrozole. In contrast, BMD remained stable in patients receiving zoledronic acid, irrespective of the endocrine therapy (tamoxifen or anastrozole).[21] Thus, although the association between AI therapy and bone loss may concern physicians prescribing AIs, in patients who experience severe bone loss necessitating clinical intervention, this can probably be easily managed with bisphosphonate therapy, or other antiresorptive agents, although further follow-up is required. Another agent undergoing evaluation is denosumab, a RANKL inhibitor that appears to be an effective agent in the setting of postmenopausal osteoporosis and in lytic bone metastases from breast cancer.[22,23]

2.8. *Quality of life*

The effect of AIs on quality of life (QoL) was studied in the ATAC, IES and MA.17 trials. The QoL subprotocol of ATAC reported that 2 years of therapy with anastrozole or tamoxifen had a similar overall impact on QoL, as assessed by the Functional Assessment of Cancer Therapy-Breast scale plus the endocrine subscale. Endocrine-related symptoms worsened initially, irrespective of therapy, and partially recovered during the 2-year assessment period.[24] Using the same assessment tools, no differences were seen between the exemestane and tamoxifen arms of the IES in the 2 years after randomization. Some endocrine-related symptoms improved during the study period (hot flushes, night sweats, gynecological and sexual problems), while other symptoms persisted (reduced libido and vaginal dryness).[25]

Over 3600 women enrolled in the MA.17 trial also participated in the QoL substudy. QoL was assessed by the Short Form 36-item Health Study (SF-36) and the Menopause-specific QoL (MENQOL) at 0, 6, 12, 24 and 36 months. Letrozole did not adversely impact on overall QoL in MA.17. Small but significant differences were reported in SF-36 physical functioning at 12 months ($p < 0.001$), bodily pain at 6 months ($p = 0.001$), and vitality at 6 and 12 months ($p = 0.005$), and in MENQOL physical domains at 12 months ($p = 0.004$). Moderate differences were seen in MENQOL vasomotor function at 6, 12, and 24 months ($p < 0.001$), and sexual function at 12 and 24 months ($p = 0.02$).[26] It is important to note that, in this trial, the effect of letrozole therapy on QoL was compared with the effect of a placebo, not tamoxifen.

2.9. *Cost-effectiveness of AI therapy*

Cost can be an important consideration, and may represent a barrier to AI use, particularly in countries where patented drugs are many times more expensive than generics, such as tamoxifen. The third-generation AIs are more expensive than tamoxifen, but their improved efficacy and tolerability can lead to savings, making AIs a cost-effective option.

Reduction in the number of patients who experience breast cancer recurrence reduces the costs associated with further therapy and the management of adverse events associated with this treatment. Early adjuvant trials showed that AIs have at least comparable tolerability to tamoxifen. The reduced incidence of some adverse events in patients taking an AI compared with tamoxifen could lead to considerable savings. In particular, thromboembolic disease requiring hospitalization and/or long-term therapy, and gynecological symptoms necessitating endometrial biopsy, were shown to be significantly reduced with AI therapy. Consistent with improved efficacy and tolerability, health economic studies have shown the cost per quality-adjusted life-year saved to be ~$26,000 for letrozole[27] and anastrozole,[28] demonstrating that AIs are a cost-effective treatment option in early breast cancer. Notably, the threshold for 'willingness to pay' in the USA is $50,000.

3. Conclusions

AIs are generally well tolerated, do not adversely affect QoL, and have better overall tolerability than tamoxifen. The AIs and tamoxifen have partially overlapping side-effect profiles, which reflect differences and similarities in the mechanisms of action of these two classes of agent. Classic symptoms of estrogen deprivation are associated with both tamoxifen and AIs. Tamoxifen acts as an estrogen agonist in some tissues, which causes some side effects that are not seen with AIs. Of particular note, thromboembolic disease and invasive endometrial cancer, which can cause considerable morbidity and mortality, were significantly lower in patients receiving an AI than in those on tamoxifen.

The estrogenic effects of tamoxifen are beneficial in some target organs, for example, protecting against bone loss in postmenopausal women, disorders of lipid metabolism and perhaps cardiac disease. AIs have no estrogenic properties. Early adjuvant studies comparing AIs with tamoxifen highlighted cardiac disease, hypercholesterolemia and bone loss as potential adverse events associated with exposure to AIs. Analysis of data from the extended adjuvant setting, comparing letrozole with placebo, has revealed that effects on cardiac tissue and lipid metabolism may, in fact, reflect a lack of the beneficial effects of tamoxifen, rather than true detrimental effects of the AIs, demonstrating the importance of considering possible effects of the comparator when assessing data from these trials. Further studies are required to determine the true effect of AIs on the cardiovascular system.

Loss of bone mass in patients receiving adjuvant AI therapy is consistent with the near-complete inhibition of estrogen synthesis by these highly effective agents. Concerns about the effect of AIs on bone could impact on the willing-

ness of physicians to prescribe AIs to postmenopausal patients, who are naturally at risk of osteoporosis. However, recent studies have emphasized monitoring and shown that bisphosphonate may protect against short-term, AI-induced bone loss.

Although AIs are more expensive than tamoxifen, savings can be made due to reduced disease recurrence and a reduction in some adverse events requiring intervention. In health economic studies, AIs have been shown to be a cost-effective treatment option. Although the long-term tolerability of AIs requires further investigation, current data demonstrate that these agents are generally well tolerated and that side effects are manageable; furthermore, their greater efficacy compared with tamoxifen indicates that the AIs are an effective treatment for HR+ early breast cancer.

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