Appraising Adjuvant Aromatase Inhibitor Therapy

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Abstract
Tamoxifen, once the gold standard adjuvant endocrine therapy for early breast cancer, is being challenged by third-generation aromatase inhibitors (AIs) that have demonstrated improved disease-free survival in a variety of adjuvant settings for early breast cancer. Tamoxifen and AIs have different safety profiles, which should allow physicians to begin to individualize treatment based on a patient’s comorbidities and risk factors. Because of its properties as a partial estrogen agonist, tamoxifen has a positive effect on serum lipids and may confer a cardioprotective benefit, as well as a beneficial effect on bone health. However, tamoxifen increases the risk for endometrial cancer and cerebrovascular/thromboembolic events. In comparison, the major side effect of AIs is increased bone loss, which may heighten the risk for osteoporotic fractures and bone pain. Because of their superior efficacy and manageable side effects, AIs are a cost-effective alternative to tamoxifen, and clinical guidelines now embrace AIs as appropriate adjuvant therapy for hormone-sensitive early breast cancer. The anticipated results of ongoing trials will provide further insights into the long-term safety and application of AI therapy in the adjuvant setting. The Oncologist 2006;11:1058–1069

Introduction
For many years, the selective estrogen-receptor modulator tamoxifen (TAM) was the standard endocrine adjuvant therapy for early breast cancer [1]. Although 5 years of adjuvant TAM therapy has been proven efficacious, reducing disease recurrence and the incidence of contralateral breast cancer by about 50% and mortality by 28% in women with estrogen-receptor–positive (ER+) tumors [2], it also has significant limitations [3]. Sixty-three percent of patients experience adverse events (AEs) [4], and studies have reported that 23%–40% of patients discontinue TAM because of tolerability issues [5–7]. Long-term TAM therapy is associated with an increased risk for hot flashes, vaginal bleeding and discharge, endometrial cancer, hysterectomy, ischemic...
cerebrovascular events, and venous thromboembolic events [2, 6, 8–10]. TAM therapy beyond 5 years is not recommended because no further benefit is derived [3], the risk of serious AEs increases, and patients may develop TAM resistance so that TAM begins to exert an agonist effect on tumors, making their prognosis worse [11, 12].

The third-generation aromatase inhibitors (AIs) anastrozole (ANA), letrozole (LET), and exemestane (EXE) are starting to replace TAM. AIs prevent estrogen synthesis by inhibiting the aromatase enzyme that converts androgens to estrogen [13]. Data on the efficacy and safety of AIs for the treatment of early breast cancer have started to be reported over the last few years. The availability of these data allows for a critical review of this therapeutic option at a time when the treatment paradigm for the management of the disease is rapidly changing. Medical organizations and oncologists have evaluated the data related to AIs, treatment guidelines have expanded recommendations for their use, and it is estimated that more than 50% of postmenopausal women with ER+ breast cancer in the U.S. are currently being treated with an AI [14–16]. This review examines safety and efficacy data for AIs and assesses their advantages and disadvantages compared with TAM. It also considers the impact of treatment options on comorbidities commonly encountered in this population.

**Efficacy of Adjuvant AI Therapy**

**Anastrozole**

ANA, a nonsteroidal AI, has been directly compared with TAM as an adjuvant treatment for breast cancer and as sequential adjuvant treatment following a few years of TAM. In the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, ANA had a significant advantage over TAM in disease-free survival (DFS) and time to recurrence at median follow-up times of 33 months, 47 months, and 68 months; this advantage increased over time [8, 17]. The combination treatment arm was dropped after the first analysis because it was no more efficacious than the TAM alone arm (although it would still be of interest to obtain some follow-up for this group of patients). Treatment with ANA significantly reduced the risk for distant metastases by 14% and contralateral breast cancer by 42% in the intent-to-treat (ITT) population compared with TAM (p = .04 and p = .001, respectively) [8]. A similar, but nonsignificant effect on distant metastases (relative risk reduction, 16%; p = .06) and a larger effect on contralateral breast cancer (relative risk reduction, 53%; p = .001) were seen in the hormone-receptor–positive subgroup. Disappointingly, there were no significant differences in overall survival (hazard ratio, 0.97; p = .7) or deaths due to breast cancer at 68 months of follow-up [8]. The small, open-label, phase III Italian Tamoxifen Anastrozole (ITA) trial and the Arimidex Nolvadex 95/Austrian Breast Cancer Study Group 8 (ARNO 95/ABCsG 8) trials are two smaller studies that have shown that switching to ANA, as a sequential therapy after 2–3 years of TAM, significantly reduced the risk for recurrence [18, 19] compared with TAM therapy only for 5 years. Recently reported results from the open-label ARNO 95 trial confirm these results [20]. At 30.1 months’ median follow-up, switching from adjuvant TAM to adjuvant ANA resulted in a 34% reduction in the relative risk for disease recurrence or death (hazard ratio, 0.66; p = .049) and a statistically significant 47% improvement in overall survival (p = .045) compared with those patients who remained on TAM. However, it is important to note that at 30.1 months of follow-up, there were low numbers of deaths in the treatment arms (15 for ANA versus 28 for TAM) in that trial.

**Letrozole**

LET, a nonsteroidal AI, has been studied in a variety of adjuvant settings as well. In the National Cancer Institute of Canada (NCIC) MA.17 trial conducted by the North American Breast Intergroup, about 5,000 postmenopausal women were randomized to either 5 years of LET therapy or placebo, following 5 years of TAM therapy [21]. The trial was closed after only 2.4 years of median follow-up when data analysis revealed the significant superiority of the results from the LET treatment arm. Those receiving LET showed an improvement in DFS earlier than anticipated (p = .00008 at the first interim analysis), with an estimated 4-year reduction in recurrence of 43% compared with placebo [21]. Updated analysis with 30 months of follow-up confirmed these findings, showing that LET, when given as an extended adjuvant therapy (i.e., after 5 years of adjuvant TAM therapy), offered a statistically significant and clinically relevant improvement in DFS (hazard ratio, 0.58; p = .00004) and a 40% reduction in distant metastases (hazard ratio, 0.60; p = .002) [22]. At a median follow-up of 30 months, LET also decreased recurrence by 55% in node-negative patients and by 39% in node-positive patients [22]. The updated analysis also showed that LET was associated with a significant survival advantage in patients with node-positive tumors, the first survival benefit seen so far with an AI in early breast cancer [22].

A retrospective analysis from local assessment of hormone receptor status in this trial also found that the effect of LET relative to placebo appears most pronounced in women with ER+/progesterone-receptor–positive (PgR+) tumors [23], and data from an analysis of four smaller cohorts of patients by randomization date (12, 24, 36, and 48 months) show a significant reduction in the risk for recurrence in the...
favor of letrozole in all four cohorts over time [24]. The data show that the DFS hazard ratios (LET/placebo) progressively decreased in favor of letrozole over 48 months, from 0.52 at 12 months to 0.19 at 48 months, and suggest that the longer the exposure to LET (at least out to 48 months), the greater the benefit for patients [24]. Finally, the results from events postunblinding from the MA.17 trial have recently been presented [25]. The MA.17 study was unblinded in 2003, and patients who were receiving placebo at that time were offered the option to switch to LET. A total of 1,655 women did so, but 613 patients decided to continue with no treatment. The results showed that patients who switched to LET from placebo did significantly better than those who continued with no treatment, in terms of all parameters evaluated: DFS, distant DFS, overall survival, and contralateral breast cancer [25]. These findings suggest that LET should be considered for most women with disease-free periods up to 5 years following adjuvant TAM, as LET has now been shown to offer a significant survival advantage even for patients who have been off TAM for a prolonged period of time.

The Breast International Group (BIG) 1-98 trial is an ongoing study in which patients are randomized to 5 years of TAM, 5 years of LET, 2 years of LET followed by 3 years of TAM, or 2 years of TAM followed by 3 years of LET [26]. The primary core analysis results included data from the monotherapy treatment arms and the first 2 years of therapy from the sequencing treatment arms (censoring data beyond treatment crossover). At 26 months of follow-up, more than 1,200 patients in the primary core analysis were followed for at least 5 years. The results showed that LET significantly improved DFS (absolute increase in 5-year DFS, 2.6%; relative risk reduction, 19%; p = .003) and reduced distant metastases (relative reduction, 27%; p = .0012) compared with TAM [26]. A trend toward a reduction in mortality was seen with LET (14%; p = .16) compared with TAM at the current follow-up period, and the significant prevention of early distant recurrence observed with LET should translate into significant mortality reduction over the longer term. Data from the supplementary analysis on the comparison of the adjuvant therapy arms (arms A and B alone; n = 4,922) of the BIG 1-98 trial are now available in the recent European Summary of Product Characteristics (SPC) label for LET in the adjuvant indication [27]. Data from the monotherapy arms continue to demonstrate, with a longer median follow-up of almost 40 months, that LET provides a significant benefit in DFS (hazard ratio, 0.80; p = .0061) and in distant DFS (hazard ratio, 0.78; p = .0195). A continuing positive trend in overall survival (hazard ratio, 0.84; p = .13) was also observed [27].

Notably, results from a central review of ER, PgR, and human epidermal growth factor receptor 2 (HER-2) in BIG 1-98, the first central review ever undertaken for an adjuvant AI trial, were recently presented, and full publication of the analysis showing a benefit of LET in all ER+ tumors irrespective of PgR status is eagerly awaited [28].

**Exemestane**

EXE, a steroidal AI with an androgen structure [29], has been studied as sequential adjuvant therapy after several years of TAM. The Intergroup Exemestane Study (IES) trial investigated the efficacy and safety of receiving EXE therapy after 2–3 years of adjuvant TAM. Results at 30.6 months of follow-up showed a significant improvement in DFS for sequential therapy with TAM followed by EXE, compared with 5 years of TAM alone (hazard ratio, 0.68; p = .00005) [30]. This significant 32% reduction in recurrence was observed regardless of nodal status and corresponded to an absolute benefit of 4.7% in DFS with EXE at 3 years postrandomization compared with the standard 5 years of TAM treatment [30]. Sequential therapy with EXE also reduced distant recurrences by 34% (hazard ratio, 0.66; p = .0004) and significantly reduced contralateral breast cancer by 56% (hazard ratio, 0.44; p = .04) compared with the standard 5 years of TAM treatment [30]. Further, while there was no significant difference in overall survival at 30.6 months of follow-up, the analysis did demonstrate a strong trend in overall survival in favor of switching to EXE. The recently presented mature results of the trial show that, at 55.7 months’ median follow-up, switching to EXE resulted in a 24% improvement in DFS (hazard ratio, 0.76; p = .0001) and a 15% difference in overall survival favoring EXE in the ITT population (hazard ratio, 0.85; p = .08) [31]. Recall that, as only patients who had successfully completed 2–3 years of tamoxifen treatment were recruited and patients who experienced an early recurrence were excluded, this trial had a selected patient population. Therefore the results from the IES cannot be compared with those from upfront trials (i.e., ATAC or BIG 1-98), for which events are included from the start of adjuvant therapy immediately following surgery. The IES results confirm that breast cancer patients who have not received an AI as initial treatment should strongly consider switching to AI therapy as soon as possible.

There is another third-generation AI, atamestane, but results of ongoing phase III trials have not been reported to date.

**Summary of Efficacy Data**

Many phase III trials (ATAC, MA-17, BIG 1-98, and IES) have shown that AIs are superior to TAM in terms of DFS [17, 21, 26, 30]. It is important to point out that while all of these are trials of AIs in the adjuvant setting, they differed

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in design, end points, and patient populations. For example, in some studies, patients were randomized after they had received 2–5 years of TAM, while in other studies, patients were randomized immediately following surgery and received no prior adjuvant TAM. Therefore, such differences preclude direct comparisons of hazard ratios among the trials.

ANA and LET have both been shown to have superior DFS compared with TAM and are better tolerated than TAM as adjuvant therapies [8, 32]. Neither drug, however, has shown a significant effect on survival, although LET demonstrated a survival gain for the node-positive subgroup. Currently, LET is the only AI approved as an extended adjuvant therapy, and it has recently been approved as an initial adjuvant therapy. ANA is also approved as initial adjuvant therapy, and EXE has recently received approval as an early sequential therapy following 2–3 years of adjuvant TAM [33].

In the switching scenario, patients receive TAM therapy for a few years. Study results indicate that switching to an AI after 2–3 years of TAM is better than continuing on TAM [18, 19, 30]. However, it should be noted that women whose disease recurs within the first 2–3 years after surgery probably have more aggressive disease, and these women are excluded from sequential trials that randomize women after they receive 2–3 years of TAM. Given the noted rates of recurrence in the first 3 years of adjuvant TAM [8] and after surgery [34], initial treatment with an AI may be a better option [8]. Interestingly, the first results from the BIG 1-98 trial show that LET has demonstrated greater benefit, especially in this population with more aggressive disease (node-positive patients). The potential benefits and risks of starting with an AI (versus TAM) or waiting to switch are being debated, but the eagerly awaited results from the sequential arms of the BIG 1-98 trial should help define the optimal treatment strategy (early adjuvant versus sequential therapy).

**Impact of Treatment on Common Comorbid Conditions**

As more agents become available for the treatment of breast cancer, there will be greater opportunities to individualize treatment by considering the presence of comorbidities and risk factors in individual patients, as well as the cost-effectiveness and effect on quality of life (QoL) of various endocrine therapies. The most common comorbidities seen in postmenopausal women with breast cancer are bone disease, joint pain, cardiovascular disease (CVD), and menopausal symptoms. Although the long-term effects of AIs on these and other comorbidities are yet to be determined, sufficient data now exist to elucidate the safety profile of AIs over 2–5 years of treatment.

**Bone Disease**

Both premenopausal and postmenopausal women with breast cancer are at heightened risk for developing osteoporosis [35], which increases the risk for bone fractures and associated pain, disability, loss of independence, and mortality [35, 36]. In all women, the disease itself can increase osteoclastic activity, causing osteoporosis and skeletal-related events, even in the absence of metastases [35], and metastatic disease can spread to the bone, causing fractures, spinal compression, bone pain, and hypercalcemia of malignancy [36].

In premenopausal women, chemotherapy-induced ovarian failure and surgical or medical ovarian ablation can cause premature menopause and bone loss [35, 37]. Premenopausal women with hormone-responsive breast cancer may also undergo adjuvant estrogen deprivation, which also increases bone loss [35, 36]. A decline in postmenopausal estrogen concentration accelerates bone loss in aging women, causing high rates of osteoporosis in postmenopausal women [38, 39], a problem only compounded by breast cancer treatments (hormonal and chemotherapy agents) that increase bone loss by directly or indirectly depleting estrogen levels [36, 40]. A large cohort study has confirmed that breast cancer treatments in women with nonmetastatic disease are associated with increased rates of osteoporosis/osteopenia due to cancer treatment–induced bone loss (CTIBL) [41]. Vitamin D deficiency caused by low exposure to sunlight, decreased synthesis in skin, and reduced intestinal absorption related to aging and limited dietary sources is known to increase bone turnover and bone loss [42], and other risk factors such as poor health status, smoking history, and alcohol abuse also may influence cancer treatment–related osteoporosis [41].

**AIs and Bone Disease**

While TAM has a beneficial effect on bone health [37], all three AIs appear to increase bone loss and, therefore, may increase the risk for fractures in the long term [43].

**Anastrozole.** Recently presented data from the ATAC bone substudy indicate that after 5 years, ANA causes bone mineral density (BMD) loss in postmenopausal women with early breast cancer, while TAM does not [44]. However, the rate of BMD decrease in the lumbar spine slowed down in years 2–5 for ANA-treated patients, and no patients with normal BMD at baseline developed osteoporosis following 5 years of ANA treatment [44]. Analyses of data from the ATAC trial showed that the incidence of joint symptoms and fractures was greater in the ANA arm than in the TAM arm (35.6% versus 29.4%; p < .0001 and 11.0% versus...
7.7%; p < .0001, respectively) [8]. Similarly, in the ARNO 95/ABCSG 8 trial, there were more fractures in patients switching to ANA (2.0%) than in patients remaining on TAM (1.0%) (p = .15) [18].

**Letrozole.** LET increases bone loss at the rate of 2%–3% per year [45]. In the BIG 1-98 trial, more patients in the LET arm had more bone fractures (odds ratio, 1.44; p = .0006) [26]. In the MA.17 trial, there was a small increase in patient-reported diagnoses of new-onset osteoporosis (8.1% for LET versus 6.0% for placebo; p = .003); however, there was a nonsignificant difference in the incidence of fractures between the two groups (5.3% for LET versus 4.6% for placebo; p = .25) [22]. Although joint and muscle complaints are more common in patients taking LET [21, 22], these adverse effects have no detrimental impact on QoL [46, 47]. The Zometa-Femara Adjuvant Synergy Trial (Z-FAST) 12-month data showed that only 8% of postmenopausal women with early breast cancer met criteria for bisphosphonate treatment at 1 year of follow-up, and suggest that while initial zoledronic acid treatment can manage CTIBL in postmenopausal women with early breast cancer receiving adjuvant LET, the majority of patients may not even require such intervention [48].

**Exemestane.** Although EXE uniquely induces both an increase in bone resorption and in bone formation [49] similar to other AIs, it has a negative effect on bone health. One year of treatment with EXE resulted in a 2%–3% loss in BMD, while TAM had no significant effect on BMD [50, 51]. After discontinuation of 2 years of EXE therapy, the significant loss in BMD normalized (lumbar spine) or stabilized (femoral neck) but still remained significantly higher than BMD loss in the placebo group [52]. In a planned comparison of 1,618 patients in the Tamoxifen and Exemestane Adjuvant Multicenter (TEAM) trial, EXE was also associated with significantly more bone and muscle aches [53]. In the IES, at 30.4 months of follow-up, patients taking EXE had a higher frequency of osteoporosis and arthralgia than patients taking TAM (7.4% versus 5.7%; p = .05, and 5.4% versus 3.6%; p < .01, respectively), although there was no significant difference in fracture rate (3.1% versus 2.3%; p = .08) [30]. The recently reported IES results at 55.7 months of follow-up, however, show a significant difference in fracture rates between the treatment arms (7.0% for EXE versus 4.9% for TAM; p = .003) [31]. Results of the bone substudy in 206 patients participating in the adjuvant IES were recently reported. After 1 year of therapy, EXE was associated with significantly greater reductions in lumbar spine and total hip BMD [51].

**Summary.** Bone loss is of special concern during long-term AI use in the adjuvant setting, because clinical trials have demonstrated that all AIs have predictable effects on bone turnover, with an approximately 2% loss in BMD per year, but the effects on fracture rates have been variable [43]. In selecting endocrine therapy, physicians and patients must weigh the higher risk for fractures associated with AIs against the higher risk for endometrial and cerebrovascular/thromboembolic morbidity associated with TAM [54]. Patients at increased risk for fracture can be readily identified, monitored, and managed proactively according to current American Society for Clinical Oncology (ASCO) treatment guidelines [37, 43, 54]. Indeed, monitoring of bone health and interventions to reduce fracture risk can be recommended for the general population, and the results from the Z-FAST study suggest that routine BMD monitoring and, if necessary, interventions with bisphosphonates are good defenses for breast cancer patients.

**CVD**

CVD is highly prevalent in the U.S.; one in five adult American women is estimated to have some form of CVD [55]. It is the main cause of death in women the U.S. [55] and in all 49 countries of Europe [56]. It is the second leading cause of death among women with breast cancer [57]. Risk factors for CVD and stroke include increasing age, race, tobacco smoke, high serum cholesterol levels, high blood pressure, diabetes mellitus, obesity/overweight, physical inactivity, and alcohol abuse [55, 56].

Postmenopausal patients with breast cancer may be at somewhat greater risk for myocardial infarction and stroke due to their menopausal status, age, increased risk for hypertension, and breast cancer therapies [58, 59]. Coronary heart disease (CHD) rates in women after menopause are two to three times greater than those in women the same age who have not reached menopause [55]. Women with breast cancer have slightly elevated rates of hypertension compared with women diagnosed with other types of cancer. Chemotherapy has been associated with an increased incidence of stroke [59, 60], while there is conflicting evidence regarding the relationship between TAM and stroke [59, 60].

TAM has been shown to have probable cardioprotective effects; for instance, a modest, but consistent 6%–28% reduction in lipid levels has been associated with TAM, as well as with several other serum estrogen receptor modulators [61]. TAM therapy not only improves lipid profiles but also reduces coronary plaques in vivo, reduces C-reactive protein, and modulates nitric oxide production [12, 62]. Thus, the treatment of breast cancer patients with TAM might be expected to reduce rates of chronic heart disease.
compared with placebo. While this cardioprotective effect of TAM has been documented in most trials [62–64], it has not been observed in others [3, 9, 65]. However, two large meta-analyses have confirmed the cardioprotective effects of TAM. A meta-analysis of 32 trials involving 52,929 patients reported that TAM significantly decreased myocardial infarction deaths compared with controls (relative risk, 0.62; 95% confidence interval, 0.41–0.93) [66]. Similarly, the recently published 15-year survival update from the Early Breast Cancer Trialists’ Collaborative Group collaborative meta-analysis of over 15,000 women also reported a lower mortality from heart disease for patients receiving TAM treatment than for patients in the control arm of the study (120 deaths versus 132 deaths; p = .06) [67].

**Als and CVD**

**Anastrozole.** In the advanced breast cancer setting, two small phase II trials have shown that ANA has no detrimental impact on lipid metabolism in postmenopausal women as first- or second-line endocrine therapy [68, 69]. In the adjuvant setting, at a median follow-up of 59 months, data from the ATAC trial reveal a higher rate of hypercholesterolemia for ANA-treated patients (9.0%) than for TAM-treated patients (3.5%) [70]. These data are difficult to interpret, however, because lipid data were collected irregularly in that trial; the visit forms did not specifically request lipid data, which were reported under the category of any other relevant medical history. Current data from the ITA switching trial also report that ANA increases total serum cholesterol and serum lipids when compared with TAM [19, 71, 72].

Regarding cardiovascular events, at 59 months of follow-up in the ATAC trial, angina pectoris was reported significantly more frequently in ANA-treated patients (2.3%) than in TAM-treated patients (1.6%), while the incidence of myocardial infarction was comparable in the two groups (1.2% for ANA versus 1.1% for TAM) [70]. At 68 months of follow-up, there was a slightly higher ischemic CVD rate when comparing ANA with TAM (4.1% for ANA versus 3.4% for TAM; p = .1) [8].

**Letrozole.** First results from the BIG 1-98 trial indicate that fewer patients in the LET arm experienced grade 3–5 thromboembolic events (odds ratio, 0.38; p < .0001), and while the overall incidence of cardiac events was similar between the two groups (4.1 versus 3.8; p = .61), slightly more experienced grade 3–5 cardiac events (2.1% versus 1.1%; p = .0003) [26, 32]. The incidence of nonfasting hypercholesterolemia (90.8% of the values were not obtained after an overnight fast) was higher in patients treated with LET compared with those receiving TAM (43% versus 19%), but the majority of reports were grade 1. Also, the difference between the arms may be a consequence of the lipid-lowering ability of TAM, as the median percent changes in cholesterol values from baseline to 6, 12, and 24 months were 0%, 0%, and −1.8% for the LET group and −12.0%, −13.5%, and −14.1% for the TAM group, respectively [32]. Studies in ovariectomized rats showed that LET had no effect on serum lipids [73]. Short courses of therapy with LET (3 and 6 months) also had no significant effect on serum lipids (total, high-density lipoprotein [HDL], or low-density lipoprotein [LDL] cholesterol) [74, 75]. In the MA.17 trial, hypercholesterolemia (16% versus 16%; p = .79) and cardiovascular events (5.8% for LET versus 5.6% for TAM; p = .76) occurred with a similar frequency in patients treated with LET and patients receiving placebo following 5 years of TAM therapy [22]. Recent results from the MA.17 lipid substudy also confirm that LET does not significantly alter lipid profiles in postmenopausal women with primary breast cancer who were treated with LET for 36 months in the extended adjuvant setting (samples were drawn under fasting conditions) [76].

**Exemestane.** Two years of adjuvant EXE therapy had no significant effect on total cholesterol or triglyceride levels but caused a modest yet significant drop in HDL cholesterol compared with placebo [77]. In another study assessing the effect of EXE on lipid profiles (n = 147), 2 years of EXE therapy resulted in slight decreases in HDL and apolipoprotein AI levels compared with patients receiving placebo; however, the effects of EXE on lipids were reversible shortly after treatment discontinuation, suggesting that EXE has no lasting detrimental impact on lipid profiles [78]. In the IES, data regarding lipid levels were not collected, but information on CVD was reported. The number of cardiovascular events (excluding myocardial infarction) was higher in patients receiving EXE than in those receiving TAM (46.2% versus 39.2%; p = .11, respectively), as was the rate of myocardial infarction (0.9% versus 0.4%; p = .02, respectively) [30, 79].

**Summary.** Serum estrogen receptor modulators such as TAM consistently have a modest lipid-lowering effect (6%–28% reduction) [80–82]; therefore, reports of cholesterol increases in trials comparing AIs with TAM may be more a consequence of losing the lipid-lowering effects of TAM rather than a result of AIs increasing serum lipid levels. Interestingly, an open, randomized, multicenter, phase I pharmacodynamic study comparing the effects of EXE, ANA, and LET on lipid profiles in healthy postmenopausal women found that at 24 weeks there were no significant
differences among the AIs with respect to their effect on total cholesterol, triglycerides, and the ratio of LDL cholesterol to HDL cholesterol, but the ratio of apolipoprotein B to apolipoprotein A-I, an indicator of an increased risk for coronary heart disease, was elevated with EXE and stayed normal with ANA and LET [83].

Cardiovascular risk factors are present in patients with breast cancer and mirror the high rates of these risks in the general population. While intertrial comparisons must always be considered with caution, the fact that the incidence of CVD has been inconsistently reported in the AI trials makes it very difficult even to compare across these studies. For instance, the measurements of ischemic CVD in the IES most likely included many cardiac AEs of limited clinical importance such as hypertension. In the ATAC trial, nonspecific requests to report AEs were collected only during treatment and 14 days post-treatment, while the BIG 1-98 trial recorded cardiac and cerebrovascular events on check-listed AE case report forms at the regular patient visits while on therapy, and after the completion of treatment, patients were followed annually and life-long. In addition, because many trials lacked a placebo control group, it is impossible to know whether some of the cardiac events reported in AI trials were a result of the loss of the protective end-organ effects of TAM or a detrimental effect of AIs on cardiac health. However, in MA.17, the only trial that actually compared an AI with placebo, there was no difference in the rate of cardiovascular events between the treatment arms. Without properly designed head-to-head trials, it is impossible to assess the precise cardiovascular risks of AI therapies, but all breast cancer patients, especially those at risk for cardiovascular events, need to be routinely monitored for CVD and managed appropriately.

Gynecological Health

Vasomotor symptoms are the most common medical complaint of perimenopausal and postmenopausal women [84] and are exacerbated by smoking [85]. Women with hot flashes are more likely to experience disturbed sleep, depressive symptoms, and significant reductions in QoL; frequent vasomotor symptoms can be disabling, affecting a woman’s social life, psychological health, sense of well-being, and ability to work [84]. Anticancer and osteoporosis prevention drugs may stimulate hot flashes and night sweats because they function partially as antiestrogens. If hot flashes are occurring more than 2–3 times per week, regardless of the cause, nonhormonal treatments should be employed [86]. Also, during menopause, the tissues of the vagina and urethra dry and thin and lead to dyspareunia (pain during sexual intercourse), vaginitis, cystitis, and urinary tract infections [87]. It is not surprising then that postmenopausal women complain of a lack of vaginal lubrication and dyspareunia significantly more often than younger women [88].

AIs and Gynecological Health

Anastrozole. In the ATAC trial, women taking ANA experienced significantly fewer hot flashes and less frequent vaginal discharge/bleeding, endometrial cancer, and hysterectomy compared with women taking TAM [8, 10]. ANA resulted in more vaginal dryness and dyspareunia than TAM; however, these side effects did not negatively affect QoL [89].

Letrozole. In the MA.17 trial, women taking LET experienced a higher frequency of hot flashes (58%) than women taking placebo (54%) but less vaginal bleeding [22]. However, an open-label, crossover study of patients intolerant of adjuvant TAM found that switching to LET was associated with a significant reduction in hot flashes [90]. Furthermore, in the BIG 1-98 trial, which compared LET with TAM as an initial adjuvant therapy, fewer patients in the LET group experienced hot flashes compared with the TAM group (33.6% versus 38.1%) [32].

Exemestane. Vaginal dryness has occurred more frequently in patients taking EXE than in patients taking TAM, while vaginal discharge and bleeding has been observed more commonly with TAM than with EXE [30, 91].

Summary. While AI therapies may increase the risk for vasomotor symptoms and vaginal dryness, many phase III trials (ATAC, MA.17, BIG 1-98, and IES) have shown that there are lower incidences of endometrial cancer and fewer vaginal bleeding/discharge events with AIs than with TAM [92, 93].

Other AEs

AIs may increase the risk for other AEs, but additional research is needed to confirm these preliminary findings. EXE has been connected with increased rates of visual disturbances [30] and diarrhea [30] and may cause steroidal androgenic side effects such as weight gain and skin reactions [94]. ANA appears to cause less weight gain than TAM [95, 96], which produces weight gain similar to that with EXE [97]. Women taking LET have reported hair thinning [98], adjuvant EXE has been associated with impaired word finding [53], and in a study comparing patients from the ATAC trial with healthy controls, patients receiving ANA showed significant impairment in tasks measur-
ing processing speed and immediate verbal memory [99]. Recently, another study has also reported that women with early breast cancer who receive adjuvant ANA therapy experience more severe impairment in cognitive function than women who receive TAM therapy [100].

**Cost-Effectiveness**

Initially, treatment with generic TAM is less expensive than with AIs [101], but this changes over time. AI-induced bone complications as well as intravenous bisphosphonate use (effective in preventing bone loss; e.g., zoledronic acid), which should reduce projected costs of bone complications caused by breast cancer and breast cancer therapies, all influence cost-effectiveness estimates [102–105]. Consequently, when the cost of TAM-induced severe AEs is also considered, the AIs appear to be a more cost-effective treatment option in the long run [106].

The cost-effectiveness of AIs is reasonable and similar to other standard treatments for early breast cancer [107–109]. Treatments that cost less than $50,000 (or £30,000) per quality-adjusted life-year (QALY) gained are generally considered to be cost-effective [109]. LET has been found to be cost-effective as an extended adjuvant therapy [108, 110]. Recent data also indicate that the cost per QALY gained with LET in U.S. and U.K. adjuvant settings is less than this widely accepted threshold [111, 112], while the incremental cost-effectiveness of ANA has been published to be higher than $50,000 [107]. However, a recently presented abstract estimates the cost per QALY gained with ANA to be lower than $50,000 [113]. Other studies indicate that switching to EXE after 2–3 years of TAM is also a cost-effective strategy in the management of early breast cancer [114, 115].

**QoL**

As breast cancer patients are living longer, issues surrounding patient tolerability and QoL become increasingly important. Early results from the ATAC and MA.17 trials and the IES suggest that all AIs have an acceptable impact on patient QoL [47, 89, 95, 116]. More recently, when QoL scores were analyzed by treatment group and age for U.S. and Canadian cohorts in the MA.17 study, the results showed that extended adjuvant LET therapy maintained QoL irrespective of a woman’s age [117]. Thus, the available data indicate that overall, the superior efficacy benefits of AIs over TAM are achieved without compromising overall QoL in the short term [46].

**Guideline Recommendations**

The latest ASCO guidelines suggest that 5 years of TAM therapy is no longer the appropriate standard adjuvant treatment for postmenopausal women with ER+ early breast cancer [15]. The ASCO Technology Assessment Panel recommends that an AI, either initially or following a period of TAM, should be included in adjuvant therapy for postmenopausal women with ER+ early breast cancer to lower the risk for tumor recurrence [15]. Similarly, the National Comprehensive Cancer Network guidelines also recommend the use of aromatase inhibition over TAM as a single agent as the preferred long-term prevention strategy for adjuvant hormonal therapy for postmenopausal women [118]. Finally, the recently published 2005 St. Gallen International Conference on Primary Therapy of Early Breast Cancer guidelines also recommend the use of AIs for the adjuvant treatment of endocrine-responsive breast cancer [16].

**Conclusions**

Each patient is unique and must be assessed individually with respect to therapy risks and benefits. A patient’s lifestyle and comorbidities, as well as current medications and their respective effects on organs or metabolic interactions, must be considered in selecting treatment. The many excess gynecological, thromboembolic, and cerebrovascular AEs experienced by TAM-treated patients would be decreased by substituting an AI for TAM [54]. Although much is yet unknown about the long-term effects of AI therapies, available data suggest that the AEs associated with AIs can be managed. Results from the Z-FAST study indicate that changes in BMD during long-term adjuvant treatment with LET can be easily monitored and ameliorated with appropriate bisphosphonate therapy. Current information seems to indicate that AIs do not have the cholesterol-lowering properties of TAM, but neither do these data indicate that AI treatment results in a significant worsening of total cholesterol concentrations. Also, although AI therapy may be associated with a slightly higher rate of cardiovascular events when compared with TAM, these slight differences are probably a reflection of the cardio-protective effect of TAM.

The optimal duration of endocrine therapy, the comparative efficacy of AIs, the benefits derived by switching from a nonsteroidal AI to a steroidal AI, and the possibility of improved efficacy with combination therapies are some as yet unanswered questions about AIs, and trials are under way that will address these issues [12, 119]. Currently, a large population of breast cancer patients may be receiving suboptimal treatment. Current data demonstrate that AIs are superior to TAM with respect to prolonging DFS and lack some of the serious toxicities of TAM therapy. All third-generation AIs are generally well tolerated, and the majority of AEs are mild to moderate. The higher rates of disease recurrence, AEs,
and premature withdrawals that occur with adjuvant TAM at 2.5 and 5 years justify the consideration for offering adjuvant therapy with an AI at the earliest opportunity [54].

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**ADDITIONAL READING**