Safety profiles of tamoxifen and the aromatase inhibitors in adjuvant therapy of hormone-responsive early breast cancer

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Adjuvant endocrine therapy plays an important role in the management of hormone-receptor-positive early breast cancer, and has increased life expectancy for millions of women. Many patients receive adjuvant treatment for at least 5 years following tumor resection, hence good long-term safety is important for endocrine agents to gain widespread acceptance. Tamoxifen has been used as adjuvant therapy for early breast cancer for many years, and safety data have been well documented, but a poor risk:benefit profile limits treatment duration to 5 years. Increased efficacy over tamoxifen and good tolerability have recently made the third-generation aromatase inhibitors (AIs) the first-choice agents for adjuvant endocrine therapy; however, it is currently not known whether AI therapy, like tamoxifen, will be limited to 5 years. Many side effects of endocrine therapy, such as hot flushes and mood disturbances, are related to estrogen deprivation and are common to tamoxifen and AIs, reflecting the mechanism of action of these drugs. In addition, tamoxifen has estrogenic effects that are beneficial in some tissues; tamoxifen lowers serum cholesterol levels and protects against bone loss and cardiovascular disease, but is also associated with potentially life-threatening side effects, such as endometrial cancer and thromboembolic disease. As AIs lack estrogenic activity, they are not associated with these serious adverse events. Clinical trials comparing AIs with tamoxifen in the adjuvant setting have shown that AIs are well tolerated and are associated with a lower incidence of gynecological symptoms and hot flushes than tamoxifen. However, AIs are associated with musculoskeletal side effects, such as arthralgia, myalgia and bone loss, but these events are preventable or manageable. The effects of AIs on lipid metabolism and the cardiovascular system are still debatable, but placebo-controlled trials provide no evidence to suggest that AIs adversely affect these systems. Furthermore, the AIs allow women to maintain a good quality of life, comparable with women receiving tamoxifen or placebo, and are a cost-effective therapeutic option. Ongoing trials will provide more information regarding the long-term effects of AI therapy and will provide comparative data on the efficacy and safety of the different AIs, thereby helping to determine the optimal treatment strategy for these highly effective and well-tolerated drugs.

Key words: aromatase inhibitors, breast cancer, hormone-responsive, safety, tamoxifen

introduction

The introduction of adjuvant therapy has significantly reduced relapses and improved survival prospects for women with early breast cancer. Endocrine therapy for hormone-receptor-positive (HR+) early breast cancer starves tumor cells of the growth-promoting effects of estrogen. Many patients receive such treatment for 5 or more years after surgery, and the long-term safety of endocrine agents used in the adjuvant setting is, therefore, very important.

Tamoxifen has been the adjuvant endocrine therapy of choice for over 30 years and abundant, mature safety data exist for this highly successful drug. Tamoxifen is generally well tolerated and side effects are mainly attributable to estrogen deprivation. However, in some tissues, tamoxifen acts as an estrogen agonist, and these estrogenic effects may be beneficial or detrimental, depending on the target organ. For example, tamoxifen has favorable effects on bone health, lipid metabolism and the cardiovascular system, but long-term tamoxifen use is also associated with serious, potentially life-threatening adverse events, including invasive endometrial cancer and thromboembolic disease. These more severe side effects contribute to the adverse risk:benefit profile associated with longer-term tamoxifen use, which limits adjuvant tamoxifen to 5 years [1].

The third-generation aromatase inhibitors (AIs), letrozole, anastrozole and exemestane, have demonstrated superior efficacy to tamoxifen in large, randomized clinical trials in postmenopausal women with HR+ early breast cancer [2–6]. On the basis of these findings, the AIs are becoming more widely used and are gradually displacing tamoxifen as the gold
standard acceptance of AIs is dependent on not only the clinical benefits gained in terms of disease recurrence, but also good long-term safety.

Current data from adjuvant trials indicate that the AIs are well tolerated, with side effects that are predominantly predictable consequences of estrogen deprivation. Some side effects, such as hot flushes, are common to AIs and tamoxifen as well as being associated with the natural menopause. Unlike tamoxifen, however, AIs do not have estrogenic effects, and the serious adverse events that can result from tamoxifen’s estrogenic actions (thromboembolic disease and endometrial cancer) are not associated with AI therapy. Although musculoskeletal events (arthralgia, myalgia and bone loss) have been associated with AI use, these events are more preventable and manageable than the serious side effects of tamoxifen. Compared with trials of adjuvant tamoxifen, follow-up from the adjuvant AI trials is relatively short, and the long-term consequences of adjuvant AI use have yet to be fully determined. However, no major tolerability concerns have been reported in any of the adjuvant AI trials.

Most trials assessing the efficacy and safety of AIs as adjuvant endocrine therapy have used 5 years of tamoxifen as the comparator. This strategy does not pose a problem when comparing side effects that are common to both classes of drug (e.g. hot flushes), but can complicate interpretation of data when considering the effects on estrogen-responsive tissues such as bone, where tamoxifen has a beneficial, estrogenic effect. Determining the true impact of estrogen depletion due to AIs on such tissues can, therefore, be difficult. Notably, one major trial, MA.17, compared AI (letrozole) therapy with placebo, making it easier to determine the true effects of AIs on all tissues. For this reason, MA.17 arguably provides the most accurate information regarding the tolerability of AIs as adjuvant therapy for early breast cancer in postmenopausal women.

### adverse events associated with tamoxifen

Tamoxifen is a selective estrogen receptor (ER) modulator that acts as an ER antagonist or a partial ER agonist in different target tissues [7, 8]. In the breast, the antitumor effects of tamoxifen are due to ER antagonist activity: tamoxifen blocks the effects of estrogen by competitively inhibiting the binding of estrogen to ERs. Estrogen deprivation due to tamoxifen can also lead to unwanted side effects, including hot flushes and mood disturbances. In other tissues, including bone, the uterus and the cardiovascular system, tamoxifen has estrogen agonistic activity, which can result in beneficial or detrimental effects, depending on the affected tissue. The side effects associated with tamoxifen are discussed in more detail below.

### gynecological effects and endometrial cancer

The estrogenic actions of tamoxifen on the genitourinary tract can result in unwanted gynecological symptoms, including vaginal bleeding, vaginal discharge and an increased risk of invasive endometrial cancer [1, 9, 10]. Data from trials comparing adjuvant tamoxifen and AIs are consistent with the previously reported gynecological effects of tamoxifen and suggest that gynecological problems are less problematic in patients on AIs than in those on tamoxifen. Vaginal bleeding and vaginal discharge were significantly less common in women receiving upfront AIs than tamoxifen in the ATAC (Arimidex, Tamoxifen, Alone or in Combination) and BIG (Breast International Group) 1-98 trials (Table 1) [4, 6]. In the IES (Intergroup Exemestane Study), fewer gynecological symptoms were reported in women who switched to exemestane after 2 years of tamoxifen therapy compared with those who continued on tamoxifen (Table 1) [3]. However, neither the combined ABCSG (Austrian Breast & Colorectal Cancer Study Group)-8/ARNO (Arimidex–Nolvadex) study nor the ITA (Italian Tamoxifen Anastrozole) study reported significant

### Table 1. Reduced incidence of gynecological symptoms and endometrial cancer with AIs in early and extended adjuvant trials [2–6, 11]

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment protocol</th>
<th>Event</th>
<th>Incidence (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>AI</td>
<td>Comparator</td>
</tr>
<tr>
<td>ATAC</td>
<td>Ana versus Tam</td>
<td>Vaginal discharge</td>
<td>3.5</td>
<td>13.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vaginal bleeding</td>
<td>5.4</td>
<td>10.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Endometrial cancer</td>
<td>0.2</td>
<td>0.8</td>
</tr>
<tr>
<td>BIG 1-98</td>
<td>Let versus Tam</td>
<td>Vaginal bleeding</td>
<td>3.3</td>
<td>6.6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Endometrial biopsies</td>
<td>2.3</td>
<td>9.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Endometrial cancer</td>
<td>0.1</td>
<td>0.3</td>
</tr>
<tr>
<td>IES</td>
<td>Tam → Exe versus Tam</td>
<td>Vaginal bleeding</td>
<td>5.8</td>
<td>9.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gynecological symptoms</td>
<td>4.0</td>
<td>5.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Endometrial cancer</td>
<td>0.21</td>
<td>0.46</td>
</tr>
<tr>
<td>ABCSG-8/ARNO</td>
<td>Tam → Ana versus Tam</td>
<td>Vaginal bleeding/discharge</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Endometrial cancer</td>
<td>0.06</td>
<td>0.43</td>
</tr>
<tr>
<td>ITA</td>
<td>Tam → Ana versus Tam</td>
<td>Gynecological symptoms</td>
<td>7.2</td>
<td>4.0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gynecological changes (including endometrial cancer)</td>
<td>1.3</td>
<td>8.4</td>
</tr>
<tr>
<td>MA.17</td>
<td>Let versus placebo</td>
<td>Vaginal bleeding</td>
<td>6.0</td>
<td>8.0</td>
</tr>
</tbody>
</table>

Ana, anastrozole; Exe, exemestane; Let, letrozole; Tam, tamoxifen; NR, not reported; IES, Intergroup Exemestane Study; ABCSG, Austrian Breast & Colorectal Cancer Study Group; ARNO, Arimidex–Nolvadex; ITA, Italian Tamoxifen Anastrozole.
differences in vaginal bleeding/discharge or gynecological symptoms between patients who switched to anastrozole after 2–3 years of tamoxifen and those who stayed on tamoxifen for 5 years [2, 5]. Furthermore, extended adjuvant letrozole therapy (following 5 years of adjuvant tamoxifen) was not associated with an excess of gynecological symptoms in the MA.17 trial, and vaginal bleeding was, in fact, significantly lower in patients taking letrozole than in patients receiving placebo (Table 1) [11].

Long-term use of tamoxifen has been associated with an increased risk of endometrial cancer. A meta-analysis of randomized trials of adjuvant tamoxifen, performed by the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG), reported a statistically significant increase in the incidence of endometrial cancer among women taking tamoxifen for approximately 5 years (ratio of incidence rates compared with placebo 2.58; 2P = 0.00001) [12]. Adjuvant tamoxifen was also associated with a significant increase in deaths from endometrial cancer (P = 0.0008) [12].

The AIs do not have estrogenic activity, and, as would be expected, fewer incidences of endometrial cancer were reported in women taking adjuvant AIs than in those on tamoxifen (Table 1) [2–6], although the difference was not statistically significant in all trials. Although endometrial cancer is a relatively rare side effect of tamoxifen, its serious nature means that women who exhibit gynecological symptoms, such as vaginal discharge or bleeding, during tamoxifen therapy should be promptly evaluated to rule out endometrial carcinoma as the cause. This requires costly, invasive investigational procedures, such as endometrial biopsies, which are unpleasant and can be distressing for the patient. The BIG 1-98 study demonstrated that giving upfront letrozole rather than tamoxifen significantly reduced the need for endometrial biopsies (2.3% of women on letrozole required an endometrial biopsy compared with 9.1% of women on tamoxifen, P < 0.0001) [6]. Upfront AI therapy could, therefore, save many patients from unnecessary stress and anxiety, and also considerably reduce the healthcare costs associated with treating adverse events resulting from adjuvant breast cancer therapy.

Thromboembolic disease

Thromboembolic disease is a well-recognized side effect of tamoxifen. An excess of venous thrombotic events (six with tamoxifen versus two with placebo) was associated with tamoxifen in an overview of breast cancer prevention trials [13], and an excess of deaths from thromboembolic events was reported in patients on tamoxifen compared with those on placebo in the EBCTCG meta-analysis of adjuvant tamoxifen trials [14]. Although rare, thromboembolic disease is a serious side effect of tamoxifen treatment, and can be difficult to treat. If not managed effectively, thromboembolic disease can be fatal; deaths due to thromboembolism in patients taking tamoxifen have been reported [1].

In the postoperative setting, thromboembolic disease was more frequently associated with tamoxifen than AIs (Table 2). Venous (2.8 versus 4.5%, P = 0.0004) and deep venous thromboembolic events (1.6 versus 2.4%, P = 0.02) were significantly more common in patients taking tamoxifen than in those taking upfront anastrozole in the ATAC trial [4], and upfront letrozole was associated with significantly fewer thromboembolic events (any grade) than tamoxifen in BIG 1-98 (1.5 versus 3.5%, P < 0.001) [6]. In the IES, switching to exemestane after 2–3 years of tamoxifen was associated with a significant reduction in the incidence of thromboembolic disease, including serious events (1.3 versus 2.4%, P = 0.007), compared with 5 years of tamoxifen [3]. Similarly, fewer patients who switched to anastrozole in the combined ABCSG-8/ARNO trial experienced thrombosis or embolism compared with patients who remained on tamoxifen, although the incidence of thromboembolic events was <1% in both trial arms (Table 2) [5].

The incidence of serious side effects, including endometrial cancer and thromboembolic disease, has been shown to increase with prolonged tamoxifen therapy [1]. Long-term toxicities, together with the development of acquired and de novo resistance, are responsible for the unfavorable risk/benefit profile seen when tamoxifen treatment is extended beyond 5 years [1]. Thus, it is recommended that adjuvant therapy with tamoxifen is limited to 5 years.

**safety profile of AIs in the adjuvant setting**

The safety and tolerability of the third-generation AIs in postmenopausal women with HR+ early breast cancer have been reported in the early (i.e. postoperative) and extended (i.e. after 5 years of tamoxifen) adjuvant settings. In trials of postoperative adjuvant therapy, the tolerability of AIs has been compared with that of 5 years of tamoxifen in two treatment strategies: an upfront substitution of tamoxifen with 5 years of AI therapy, and a therapy switch strategy, in which 2–3 years

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**Table 2.** The incidence of thromboembolic disease is greater in patients taking tamoxifen than in those on AIs in early adjuvant trials [3–6]

<table>
<thead>
<tr>
<th>Trial</th>
<th>AI</th>
<th>Adverse event</th>
<th>AI (%)</th>
<th>Tamoxifen (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATAC</td>
<td>Anastrozole</td>
<td>Venous thromboembolic events</td>
<td>2.8</td>
<td>4.5</td>
<td>0.0004</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Deep venous thromboembolic</td>
<td>1.6</td>
<td>2.4</td>
<td>0.02</td>
</tr>
<tr>
<td>BIG 1-98</td>
<td>Letrozole</td>
<td>Thromboembolic events</td>
<td>1.5</td>
<td>3.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IES</td>
<td>Exemestane</td>
<td>Thromboembolic disease</td>
<td>1.0</td>
<td>1.9</td>
<td>0.003</td>
</tr>
<tr>
<td>ABCSG-8/ARNO</td>
<td>Anastrozole</td>
<td>Serious thromboembolic events</td>
<td>1.3</td>
<td>2.4</td>
<td>0.007</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Embolism</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>0.064</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thromboses</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>0.034</td>
</tr>
</tbody>
</table>
of tamoxifen is followed by an AI for the remainder of the 5-year treatment period. The MA.17 trial reported on the safety of extended adjuvant letrozole compared with placebo. AIs were generally well tolerated across all adjuvant trials, with side effects being predictable and mostly consistent with estrogen deprivation.

hot flushes
Hot flushes are a typical symptom of estrogen deprivation, are common to tamoxifen and AIs, and were reported in approximately 40% of all patients across early adjuvant trials. In upfront trials, the incidence of hot flushes was significantly lower in patients taking AIs than in those on tamoxifen. In the ATAC trial, 35.7% of patients receiving anastrozole reported hot flushes compared with 40.9% in the tamoxifen arm ($P < 0.0001$) [4]. Similarly, in the BIG 1-98 trial, letrozole was associated with a significantly lower incidence of hot flushes than tamoxifen (33.5 versus 38%, $P < 0.001$) [6]. In therapy switch trials, the incidence of hot flushes was similar in patients taking continuous tamoxifen and in those who switched to exemestane (39.6 versus 42%, $P = 0.28$) [3] or anastrozole (48 versus 50%, $P = 0.32$) [5]. In the extended adjuvant setting, with placebo as the comparator, letrozole was, unsurprisingly, associated with an increase in hot flushes (58 versus 54%, $P = 0.003$) [11].

bone loss
Bone loss is a predictable consequence of estrogen deprivation. Accelerated loss of bone mass occurs during the menopause as a result of naturally decreasing estrogen levels, putting women at risk of osteoporosis and fracture. In addition to natural menopausal bone loss, postmenopausal women with a diagnosis of breast cancer are at greater risk of osteoporosis and fracture than healthy women of similar age [15], suggesting an inherent link between bone loss and breast cancer. Furthermore, many breast cancer treatments, including AIs and chemotherapy, are associated with additional bone loss and an increased risk of osteoporosis and fracture [16]; in contrast, tamoxifen protects against bone loss.

In all early adjuvant trials, AIs were associated with a higher incidence of osteoporosis and/or fractures, irrespective of the treatment strategy (Table 3). In the BIG 1-98 trial, more patients taking upfront letrozole experienced a fracture compared with those on tamoxifen (5.7 versus 4.0%, $P < 0.001$) [6]. Similarly, in ATAC, upfront anastrozole was associated with a significantly higher incidence of fractures (11.0%) than tamoxifen (7.7%, $P < 0.0001$) in the overall trial population [4]. In the accompanying ATAC bone subprotocol, over 5 years of treatment, patients receiving anastrozole experienced significantly greater loss of bone mineral density (BMD) than those on tamoxifen at the hip (treatment effect $-7.4$, $P < 0.0001$) and lumbar spine (treatment effect $-8.1$, $P < 0.0001$). Loss of BMD appeared to slow down in years 2–5 and no patients who had normal bone mass at baseline became osteoporotic after 5 years of anastrozole. Levels of the biochemical marker of bone resorption, NTx (cross-linked N-telopeptides of type 1 collagen), increased by 12.86% over 1 year and appeared to be correlated with lumbar spine BMD loss [17].

In the interim analysis of the IES, switching to exemestane was associated with a greater incidence of osteoporosis than remaining on tamoxifen (7.4 versus 5.7%, $P = 0.05$) [3]. Fractures were more common in the exemestane group (3.1 versus 2.3%, $P = 0.08$), and this difference became statistically significant (7.0 versus 4.9%, $P = 0.003$) with longer follow-up [18]. The IES bone substudy revealed that switching to exemestane was also associated with a significant decrease in BMD at the lumbar spine ($–3.2$ versus $–0.2\%$, $P < 0.001$) and total hip ($–2.1$ versus $–0.6\%$, $P < 0.001$), and a significant increase in markers of bone resorption [19]. Comparable results were recently reported in a similar, separate study: a marked increase in bone turnover markers and a reduction in BMD were seen in patients with breast cancer who switched to exemestane compared with those who remained on tamoxifen [20]. In the ABCSG-8/ARNO combined analysis, significantly more fractures were seen in patients who switched to anastrozole than in those who remained on tamoxifen (2 versus 1%, $P = 0.015$) [5].

Tamoxifen acts as a partial ER agonist in bone, protects against bone loss [21], and increases BMD in healthy postmenopausal women [22] and patients with breast cancer [23, 24]. This beneficial effect of tamoxifen on bone should be considered when comparing treatment arms in adjuvant trials of AIs with tamoxifen as the comparator. In the MA.17 extended adjuvant trial, compared with placebo, letrozole therapy was associated with an increase in new, self-reported osteoporosis (8.1 versus 6.0%, $P = 0.003$), but this did not translate into a significant increase in the risk of fracture (5.3% letrozole versus 4.6% placebo, $P = 0.25$) [11]. In a companion study to MA.17, which measured bone turnover markers and BMD, 24 months of treatment with letrozole caused a small but significant decrease in total hip ($–3.6$ versus $–0.7\%$, $P = 0.044$) and lumbar spine ($–5.35$ versus $–0.70\%$, $P = 0.008$) BMD compared with placebo [25]. A randomized, placebo-controlled study in patients with early breast cancer showed a mean annual BMD loss of 2.17% with exemestane (compared with

### Table 3. Frequency of osteoporosis and/or fractures reported in early adjuvant trials [2–6]

<table>
<thead>
<tr>
<th>Trial</th>
<th>Follow-up (months)</th>
<th>AI</th>
<th>Comparator</th>
<th>Event</th>
<th>AI versus ref. (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATAC</td>
<td>68</td>
<td>Anastrozole</td>
<td>Tamoxifen</td>
<td>Fracture</td>
<td>11.0 versus 7.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>BIG 1-98</td>
<td>26</td>
<td>Letrozole</td>
<td>Tamoxifen</td>
<td>Fracture</td>
<td>5.7 versus 4.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IES</td>
<td>31</td>
<td>Exemestane</td>
<td>Tamoxifen</td>
<td>Fracture/osteoporosis</td>
<td>7.4 versus 5.7</td>
<td>0.05</td>
</tr>
<tr>
<td>ABCSG-8/ARNO</td>
<td>28</td>
<td>Anastrozole</td>
<td>Tamoxifen</td>
<td>Fracture</td>
<td>2 versus 1</td>
<td>0.015</td>
</tr>
<tr>
<td>ITA</td>
<td>36</td>
<td>Anastrozole</td>
<td>Tamoxifen</td>
<td>Fracture</td>
<td>1.0 versus 1.3</td>
<td>0.6</td>
</tr>
</tbody>
</table>
1.84% with placebo, \( P = \) not significant) in the lumbar spine and 2.72 versus 1.48% (\( P = 0.024 \)) in the femoral neck. These changes were partially reversed during a 1-year follow-up period [26].

In light of the association between AIs and bone loss, postmenopausal women taking adjuvant AIs clearly require lifelong management of their bone health [27]. All patients should undergo BMD screening before starting AI therapy, and should have regular bone health assessments thereafter. Several methods for measuring BMD are available, but DEXA (dual energy X-ray absorptiometry) is a rapid, non-invasive and painless technique that remains the gold standard for baseline measurement and subsequent monitoring during treatment [28].

In 2003, the American Society of Clinical Oncology (ASCO) published guidelines for the management of bone health in patients with breast cancer, which recommend annual BMD screening for all affected women [29]. Lifestyle advice, dietary vitamin D and calcium supplementation are recommended in cases of mild-to-moderate bone loss, and bisphosphonate therapy for severe bone loss. Recently, data from the Z-FAST and ZO-FAST trials have suggested that the bisphosphonate, zoledronic acid, may prevent and/or treat AI-induced bone loss in postmenopausal women with breast cancer [30, 31]. Thus, AI-associated bone loss is a predictable and manageable event and may be preventable, allowing women to benefit from AI therapy while being protected against the increased risk of osteoporosis and fracture. The management of bone loss is discussed in detail by Dr Monnier elsewhere in this supplement.

**arthralgia and myalgia**

Arthralgia and myalgia are reported by a significant proportion of women taking AIs. Although the etiology of these complications is unknown, they are thought to be related to estrogen deprivation [32]. In adjuvant trials, AI therapy was associated with an increase in the incidence of arthralgia and/or myalgia when compared with tamoxifen or placebo.

In ATAC, more women taking anastrozole reported arthralgia than women taking tamoxifen (35.6 versus 29.4%, \( P < 0.0001 \)) [4]. Significantly more arthralgia (20.3 versus 12.3%, \( P < 0.001 \)), but not myalgia (6.4 versus 6.1%, \( P = 0.61 \)), was reported in the letrozole arm compared with the tamoxifen arm in the BIG 1-98 study, although most events were low grade. Switching to exemestane or anastrozole was also associated with a higher incidence of arthralgia/myalgia than continued tamoxifen therapy for 5 years [3, 5]. Compared with patients on placebo, the incidence of arthralgia (25 versus 21%, \( P < 0.001 \)) and myalgia (15 versus 12%, \( P = 0.004 \)) was higher in women receiving letrozole in the MA.17 trial [11]. Although common side effects, muscle and joint pain are generally manageable with physical therapies or analgesics, and the management of these symptoms is discussed by Dr Monnier elsewhere in this supplement.

**lipid metabolism and cardiovascular disease**

The effect of AIs on the cardiovascular system is a matter of ongoing debate, and further investigation is required. Data from adjuvant trials comparing AIs with tamoxifen have suggested a possible association between AIs and cardiovascular disease, although the number of events on which to base such an association was very low in all trials. Furthermore, the type and severity of adverse events recorded, as well as data collection methods, differed widely between trials, making it difficult to assess the true effect of AIs on cardiovascular health.

For example, in BIG 1-98, predefined cardiovascular events were recorded by checking specific boxes on case report forms. In contrast, in the ATAC trial, cardiovascular events were recorded when reported by patients following a non-specific request for adverse event reports by the investigators, but no prespecified checklists were used. It is also important to note that tamoxifen has a cardioprotective effect: a meta-analysis of 32 trials indicated that the incidence of, and deaths from, myocardial infarction were lower among women taking tamoxifen than women in control groups [33]. A small, non-significant increase in the number of ischemic cardiovascular events was reported in patients receiving anastrozole compared with tamoxifen in the ATAC trial (4.1 versus 3.4%, \( P = 0.11 \)) [4]. In BIG 1-98, the overall incidence of cardiac events did not differ between patients taking letrozole and tamoxifen (4.1 versus 3.8%, \( P = 0.61 \)). There was a slightly higher incidence of grade 3–5 cardiac events in the letrozole group, but the numbers were small (2.1 versus 1.1%, \( P < 0.001 \)) [6]. In the IES, no significant difference was seen in the incidence of cardiovascular disease (excluding myocardial infarction) between patients who switched to exemestane and patients who continued on tamoxifen (42.6 versus 39.2%, \( P = 0.11 \)). Exemestane did not cause an increase in the incidence of myocardial infarction compared with tamoxifen (1.0 versus 0.4%, \( P \) value not reported) [3]. Similarly, switching to anastrozole did not significantly increase the incidence of myocardial infarction in the ABCSG-8/ARNO trial [5] or cardiovascular disease in the ITA trial [2].

Importantly, in the MA.17 trial, which compared an AI with placebo and therefore assessed the true effects of an AI on the cardiovascular system, letrozole did not increase the risk of cardiovascular disease (5.8 versus 5.6%, \( P = 0.76 \)) (Figure 1) [11]. As the estrogenic effects of tamoxifen offer some

![Figure 1](image-url)
cardioprotection, it is likely that the apparent increase in cardiovascular events reported in adjuvant AI trials reflects the lack of this protective effect in patients taking AIs. Data from studies in the early adjuvant setting have suggested that there may be an association between AI therapy and changes in serum lipid profiles. In the ATAC trial, hypercholesterolemia occurred more frequently in patients who received upfront anastrozole than in patients randomized to tamoxifen (9.5 and 3.0%, P value not reported), although lipid data were not collected systematically [34]. More patients taking upfront letrozole (43.6%) than tamoxifen (19.2%) in BIG 1-98 were reported to have hypercholesterolemia during treatment, although about 80% of events were grade 1 in both treatment arms (35.1 and 17.3%, respectively) [6]. Concerns have been raised regarding lipid data collection methods, which may affect the interpretation of these findings. Most of the lipid measurements in BIG 1-98 were performed on samples from non-fasting patients, and samples were analyzed locally. Furthermore, at any scheduled 6-monthly visit, a patient with a plasma cholesterol level above the normal range would be recorded as having hypercholesterolemia, and a return to the normal range at the next visit did not alter this classification. Thus, the incidence of hypercholesterolemia reported in this trial may not be an accurate reflection of the effect of letrozole (or tamoxifen) on lipid levels. Longitudinal analysis of serum cholesterol levels in patients in BIG 1-98 revealed that the median change from baseline at 6, 12 and 24 months was 0.0, 0.0 and −1.8% in the letrozole group, and −12.0, −13.5 and −14.1% in the tamoxifen group [6]. Hence, mean plasma cholesterol levels remained stable for the duration of the study in patients receiving letrozole, and initially decreased in the tamoxifen arm, remaining stable thereafter (Figure 2) [35]. This finding is consistent with the known lipid-lowering effect of tamoxifen therapy [36, 37].

Of the trials investigating a therapy switch strategy, only ITA assessed serum lipid levels and reported that lipid metabolism disorders were more common in patients who switched to anastrozole than in those who remained on tamoxifen (8.1 versus 1.4%, P = 0.01) [2].

In the same way that the cardioprotective activity of tamoxifen may exaggerate the observed effect of AIs on cardiovascular disease, the lipid-lowering effects of tamoxifen make it difficult to determine the true effect of AIs on lipid metabolism in trials of postoperative adjuvant therapy. Data from several other studies do not support an association between AI therapy and hypercholesterolemia. A pilot study of letrozole therapy in postmenopausal women previously treated for benign breast disease or ductal or lobular carcinoma in situ did not cause significant changes in serum levels of total cholesterol, high-density lipoprotein (HDL) cholesterol or low-density lipoprotein (LDL) cholesterol after 3 months of therapy [38]. A report of neoadjuvant anastrozole therapy in postmenopausal patients with HR+ breast cancer showed no detrimental effects of anastrozole on lipid parameters after 3 months of treatment [39]. Similarly, in a randomized, placebo-controlled study of letrozole in healthy postmenopausal women, no significant differences in lipid profile (total cholesterol, HDL cholesterol, LDL cholesterol or triglycerides) were seen between the two study groups following 6 months of treatment [40]. Furthermore, 12 weeks of adjuvant anastrozole treatment in postmenopausal Japanese women with HR+ early breast cancer resulted in a reduction in triglyceride levels and an increase in HDL cholesterol levels, both of which are considered beneficial effects [41].

The MA.17 trial, comparing letrozole with placebo as adjuvant therapy in postmenopausal women who had previously completed tamoxifen, reported no difference in the incidence of hypercholesterolemia between patient groups (16 versus 16%, P = 0.79) [11]. This finding was confirmed by the MA.17L lipid substudy, in which patients recruited to the main MA.17 trial consented to have lipid parameters (total cholesterol, HDL cholesterol, LDL cholesterol, lipoprotein A

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**Figure 2.** Effect of letrozole versus tamoxifen on serum cholesterol levels [35]. (Reprinted with permission from Elsevier from Perez EA. The balance between risks and benefits: Long-term use of aromatase inhibitors. Eur J Cancer Suppl 2006; 4: 19.)
and triglycerides) measured at 6 months, 12 months and then yearly until the completion of therapy \[42\]. Small differences in the percent changes from baseline between the letrozole and placebo groups were seen only for HDL cholesterol at 6 months (+1.5% versus +4.3%, \(P = 0.049\)), LDL cholesterol at 12 months (+27.7% versus +21.5%, \(P = 0.033\)) and triglycerides at 24 months (+11.9% versus −1.3%, \(P = 0.036\)) (Table 4). At all other timepoints, no significant differences in lipid parameters were seen between the two groups.

A study comparing 2 years of adjuvant exemestane with placebo in postmenopausal women with early breast cancer reported no difference in total cholesterol, LDL cholesterol or triglycerides between the treatment arms. Furthermore, risk factors for cardiovascular disease, such as homocysteine levels and coagulation factors, were not significantly altered by exemestane treatment \[43\].

Early results from the LEAP (Letrozole, Exemestane, Anastrozole Pharmacodynamics) study suggest that AIs do not have detrimental effects on serum lipids in healthy postmenopausal women \[44\]. This study, which is the first direct comparison of letrozole, anastrozole and exemestane, shows similar effects of all AIs on serum lipid profiles.

In summary, the effects of AIs on lipid metabolism and the cardiovascular system observed in trials of postoperative adjuvant therapy probably reflect the absence of the beneficial, estrogenic effects of tamoxifen rather than any detrimental effect of AIs. Available data do not support an association between AIs and an increased risk of cardiovascular disease or a deleterious effect on lipid metabolism.

**quality of life**

Women taking postoperative endocrine therapy are free of clinical disease, and it is therefore important that adjuvant treatment allows them to maintain a good quality of life (QoL).

Substudies were performed in the IES, ATAC and MA.17 trials to determine, in detail, changes in QoL in patients on AIs. These substudies showed that, overall, AIs do not impact adversely on QoL compared with tamoxifen or placebo.

In the ATAC subprotocol, QoL was assessed using the Functional Assessment of Cancer Therapy-Breast scale plus the Endocrine Subscale: 2 years of anastrozole or tamoxifen therapy had a similar overall impact on QoL \[45\]. Endocrine-related symptoms worsened initially, regardless of the therapeutic agent, and partially recovered over the 2-year assessment period. Using the same assessment tools, no differences in QoL were seen in patients taking exemestane or tamoxifen in IES in the first 2 years after randomization \[46\]. Some endocrine-related symptoms (hot flushes, night sweats and gynecological and sexual problems) improved during the study period, while other symptoms (reduced libido and vaginal dryness) persisted.

In the MA.17 trial, QoL was assessed at 0, 6, 12, 24 and 36 months using the Short Form 36-item Health Study (SF-36) and the Menopause-specific Quality of Life Questionnaire (MENQOL) \[47\]. Compared with placebo, letrozole did not adversely affect overall QoL. A small but significant deterioration in QoL was reported with letrozole in SF-36 physical functioning at 6 and 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 in favor of placebo were also seen in MENQOL vasomotor function at 6, 12 and 24 months (\(P < 0.001\)) and sexual function at 12 and 24 months (\(P = 0.02\)) \[47\].

**safety profiles of the individual AIs**

Current data do not appear to suggest any differences in safety profile between the third-generation AIs, despite differences in their chemical structure and mode of action. Letrozole and anastrozole are non-steroidal triazoles that competitively inhibit estrogen synthesis by binding reversibly to the cytochrome P450 moiety of aromatase. In contrast, exemestane is a steroidal compound that binds irreversibly to the catalytic site of aromatase, inhibiting enzyme activity. Regardless of these differences, letrozole, anastrozole and exemestane cause near-complete inhibition of circulating endogenous estrogen in postmenopausal women within 2–4 days of starting therapy \[48\], and all three agents are associated with the same predictable consequences of estrogen deprivation. Direct comparative data on the efficacy and safety of the different AIs do not currently exist, and ongoing clinical trials are comparing the efficacy and safety of different AIs in head-to-head studies.

The FACE (Femara versus Anastrozole Clinical Evaluation) trial is a multicenter, phase III, open-label, randomized study comparing letrozole and anastrozole in postmenopausal women with HR+ node-positive early breast cancer. Patients (\(n = 4000\)) will be randomized to either anastrozole or letrozole for 5 years, within 12 weeks of undergoing surgery or within 4 weeks of completing adjuvant chemotherapy. The primary endpoint is disease-free survival, with secondary endpoints of overall survival, time to distant metastases and time to contralateral breast cancer, and a comparison of the safety

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**Table 4.** Effect of extended adjuvant letrozole therapy on serum lipid levels, compared with placebo, in the lipid substudy of MA.17 (MA.17L) (Adapted from \[40\])

<table>
<thead>
<tr>
<th>Serum lipid</th>
<th>Treatment duration (months)</th>
<th>% change from baseline, mean (SD)</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Letrozole</td>
<td>Placebo</td>
<td></td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>6</td>
<td>13.6 (12.5)</td>
<td>12.5 (14.1)</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>14.5 (14.9)</td>
<td>11.1 (15.6)</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>13.3 (14.7)</td>
<td>10.2 (18.4)</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>10.5 (16.4)</td>
<td>8.4 (24.5)</td>
</tr>
<tr>
<td>HDL</td>
<td>6</td>
<td>1.5 (15.5)</td>
<td>4.3 (13.4)</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>3.1 (16.4)</td>
<td>3.2 (17.0)</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>1.2 (18.7)</td>
<td>6.5 (29.5)</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>2.1 (23.4)</td>
<td>12.9 (43.0)</td>
</tr>
<tr>
<td>LDL</td>
<td>6</td>
<td>25.4 (23.7)</td>
<td>23.4 (25.1)</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>27.7 (27.4)</td>
<td>21.5 (29.8)</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>23.1 (27.4)</td>
<td>22.0 (33.0)</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>20.7 (26.0)</td>
<td>18.2 (43.6)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>6</td>
<td>5.1 (43.5)</td>
<td>1.9 (45.6)</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>3.5 (41.0)</td>
<td>6.4 (71.3)</td>
</tr>
<tr>
<td></td>
<td>24</td>
<td>11.9 (44.3)</td>
<td>–1.3 (42.2)</td>
</tr>
<tr>
<td></td>
<td>36</td>
<td>8.4 (47.0)</td>
<td>3.1 (35.8)</td>
</tr>
</tbody>
</table>
and tolerability of letrozole and anastrozole. The efficacy and safety of anastrozole and exemestane are being directly compared in over 6800 women with HR+ breast cancer (node-positive or node-negative) in the ongoing MA.27 trial.

**AI treatment strategies and safety**

Safety is an important factor to be considered when deciding which treatment strategy will be most beneficial to individual patients. To date, no major differences in tolerability have emerged between upfront use of an AI and switching from tamoxifen to an AI, although the different treatment strategies have not yet been compared directly.

Tamoxifen, although generally well tolerated, is associated with endometrial cancer and thromboembolic events, which are complications that can be largely avoided by upfront AI therapy. However, unlike the AIs, tamoxifen has some estrogen-related, favorable effects: lipid-lowering properties, a cardioprotective effect and a protective effect on bone. This may suggest that taking tamoxifen for 2–3 years before switching to an AI could provide some benefits for the patient, particularly with respect to bone health. However, the incidences of osteoporosis, fractures and cardiovascular events were increased in patients receiving an AI regardless of the treatment protocol used, indicating that, although using tamoxifen upfront may delay AI-associated effects, the benefits do not persist beyond the duration of therapy. This lack of a carry-over effect of tamoxifen does not support the use of switching therapy over upfront AI treatment from a safety perspective. Direct comparison of upfront substitution and sequential therapy strategies is needed to determine whether one treatment strategy has any significant benefits over the other. The results of the sequential arms of BIG 1-98 are anticipated in 2007/8 and, as patients were randomly assigned to all four treatment arms after surgery (5 years’ tamoxifen; 5 years’ letrozole; 2 years’ letrozole followed by 3 years’ tamoxifen; 2 years’ tamoxifen followed by 3 years’ letrozole), this unique trial will generate comparative data on upfront and sequential treatment strategies in the same patient population.

**cost-effectiveness of adjuvant AI therapy**

The cost-effectiveness of a therapeutic intervention is determined by several factors, including the cost of treating side effects. Although purchase costs with tamoxifen are lower than those with AIs, the reduced number of serious and difficult-to-treat side effects seen with AIs should lead to savings in the overall costs of therapy. In particular, AI therapy has been shown to lead to significant reductions in thromboembolic disease requiring hospitalization and/or long-term therapy, and a reduced need for investigation of gynecological symptoms by endometrial biopsy [6]. In addition, AIs prevent many disease recurrences that occur despite tamoxifen therapy, which also leads to savings. AIs are also less expensive than many other accepted new treatments for breast cancer, including taxanes and targeted therapies such as trastuzumab. AIs have been shown to be a cost-effective treatment option in upfront and therapy switch strategies, with incremental medical costs per quality-adjusted life-year within acceptable thresholds [49–54].

**discussion**

Overall, the AIs and tamoxifen are well-tolerated adjuvant therapies for HR+ early breast cancer in postmenopausal women. Both classes of drug effectively inhibit tumor growth by estrogen deprivation and this is reflected in their partially overlapping side-effect profiles: AIs and tamoxifen are associated with typical symptoms of estrogen deficiency, such as hot flushes, which are also a consequence of the natural menopause. The differences in the safety profiles of these agents reflect their different mechanisms of action. Tamoxifen, in addition to its ER antagonist actions, has estrogenic effects that can be beneficial in some tissues, including bone and the cardiovascular system, but deleterious in others, resulting in an increased risk of endometrial cancer and thromboembolic disease. In contrast, the AIs have no estrogenic effects and are not, therefore, associated with an increased risk of these potentially life-threatening adverse events.

The side effects that are associated with AIs are generally more manageable than those seen with tamoxifen. Arthralgia and myalgia are commonly reported by patients receiving AIs, but are generally low grade and can be successfully managed without invasive intervention in the majority of cases. Bone loss is a predictable consequence of estrogen deprivation, and physicians should assess the bone health of patients eligible for AI therapy and monitor bone health closely in those taking AIs, particularly in individuals at increased risk of osteoporosis. The ASCO guidelines for the management of patients with breast cancer at risk of osteoporosis include the use of bisphosphonates in appropriate cases.

Although data from adjuvant trials comparing AIs and tamoxifen suggest that the AIs may be associated with increased incidences of cardiovascular disease and hypercholesterolemia, it is probable that these findings reflect the fact that AIs lack the cardioprotective and lipid-lowering effects of tamoxifen. This suggestion is supported by data from MA.17 and other placebo-controlled studies, which do not provide any evidence for a detrimental effect of AIs on the cardiovascular system or lipid metabolism.

Adjuvant AI therapy did not adversely affect QoL in tamoxifen- or placebo-controlled studies, so the benefits of adjuvant AI therapy can be obtained without a significant negative impact on patients’ lives. Tamoxifen therapy is limited to 5 years, and, thus, in clinical trials comparing AIs and tamoxifen, the duration of AI treatment has also been limited to 5 years. However, there is no evidence to suggest that AI therapy should be stopped at 5 years, and trials are ongoing to assess the risks and benefits of extending AI treatment for up to 10 years. Longer follow-up and additional studies will provide further information on the optimum treatment duration of adjuvant AI therapy, from the efficacy and safety standpoints.

Although direct comparisons are lacking, consideration of existing safety data from trials of the third-generation AIs in the adjuvant setting has not revealed any differences between the individual AIs or between the different treatment strategies.
(upfront and therapy switch) studied to date. Ongoing trials will provide comparative data on the different AIs and treatment strategies, and help to determine the optimum treatment strategy for adjuvant AI therapy from both a safety and efficacy perspective.

conclusions

AIs are a well-tolerated adjuvant therapy for postmenopausal women with early breast cancer. No apparent differences exist between the AIs or between treatment strategies, although direct comparative data are awaited. The side effects associated with AI therapy are predictable and generally more preventable and manageable than those associated with tamoxifen. Health economic studies indicate that the AIs are a cost-effective option regardless of the treatment strategy used, achieving savings due to prevention of recurrences and serious side effects, and the treatment of these events. Data from ongoing trials, including longer follow-up, will provide further information regarding the long-term safety profile of these effective and well-tolerated agents.

disclosures

Professor Perez has reported that she has received research funding from Novartis.

references

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