COMMENTARY

Defining the role of aromatase inhibitors in the adjuvant endocrine treatment of early breast cancer

Aman Buzdar a, Rowan Chlebowski b, Jack Cuzick c, Sean Duffy d, John Forbes e, Walter Jonat f and Peter Ravdin g on behalf of the International Aromatase Inhibitor Expert Panel

a M.D. Anderson Cancer Center, Houston, TX, USA
b Los Angeles Biomedical Research Institute at the Harbor-UCLA Medical Center (LA BioMed), Los Angeles, CA, USA
c Wolfson Institute of Preventive Medicine, London, UK
d St. James’ University Hospital, Leeds, UK
e University of Newcastle, Mater Hospital, New South Wales, Australia
f University of Kiel, Kiel, Germany
g University of Texas Health Science Center, San Antonio, TX, USA

Address for correspondence: Aman U. Buzdar, M.D., Professor of Medicine, Breast Medical Oncology, The University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 1354, Houston, TX 77030, USA. Tel.: +1-713-792-2817; Fax: +1-713-794-4385; email: abuzdar@mdanderson.org

Key words: Adjuvant – Aromatase – Breast cancer – Oestrogen – Postmenopausal – Switching – Tamoxifen

ABSTRACT

Background: Over the past few years, data have been published concerning the relative efficacy and safety profiles of tamoxifen and the aromatase inhibitors (AIs) in the adjuvant therapy setting for women with early hormone receptor-positive breast cancer. Recently, debate has centred around trials which have studied primary tamoxifen and AI therapy, switching and sequencing strategies and extended adjuvant therapy.

Methods: Here, a group of 24 breast cancer experts review efficacy and safety data from the recent major trials investigating tamoxifen and the third-generation AIs in postmenopausal women, which have challenged the perception of tamoxifen as optimum adjuvant endocrine therapy. Data from the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial, Breast International Group (BIG) 1-98 study, National Cancer Institute of Canada MA 17 trial, Intergroup Exemestane Study (IES), Italian Tamoxifen Anastrozole (ITA) trial, Austrian Breast and Colorectal Cancer Study Group (ABCSG) Trial 8 and Arimidex-Nolvadex (ARNO) 95 are considered to provide a rational interpretation of the impact of these data on current practice, and to highlight areas where further investigation is needed.

Conclusion: We can be confident that AIs represent superior adjuvant endocrine treatment to tamoxifen in postmenopausal women, either as initial therapy or as an alternative for women who have started adjuvant therapy with tamoxifen. However, there remain issues regarding the best way to use AIs, such as the optimal length of AI treatment and how a sequence of tamoxifen followed by an AI compares with AI monotherapy; these will require further data to resolve.
Introduction

In recent years, a large body of data relating to aromatase inhibitors (AIs) and tamoxifen in the adjuvant endocrine therapy of hormone-responsive early breast cancer have been published. However, as statistically significant differences between these agents in terms of overall survival would take many years to appear, current evidence relies upon measures such as disease-free and recurrence-free survival as early indicators of efficacy. The data therefore require careful interpretation to determine the extent of benefit with each therapy, especially where different treatment strategies are employed. In particular, data from the ‘Arimidex’, Tamoxifen, Alone or in Combination (ATAC) trial\(^1\), the Breast International Group (BIG) 1-98 study\(^2\), the Italian Tamoxifen Anastrozole (ITA) trial\(^3\), the Intergroup Exemestane Study (IES)\(^4\), the combined analysis of the Austrian Breast and Colorectal Cancer Study Group (ABCsG) Trial 8 and the Arimidex-Nolvadex (ARNO) 95 trial\(^5\), the National Cancer Institute of Canada MA 17 trial\(^6\) and ABCsG Trial 6a\(^7\) have challenged the position of 5 years’ tamoxifen as optimal adjuvant endocrine therapy for postmenopausal women.

Here we present a review and interpretation of the various trials relating to different adjuvant treatment strategies for postmenopausal women, and the safety issues arising from the use of AIs and tamoxifen in the adjuvant setting. This document arose from discussion of the available data at the Breast Cancer Round Table meeting in Houston, Texas on 5–6 December 2005. Twenty-four experts from the USA, UK, France, Germany, Spain, Italy, Australia, Sweden, Belgium, China and Brazil discussed and critiqued the data, and provided their considered opinions. We present our views as a series of statements which were agreed upon at the meeting, together with supporting evidence and details of the discussion around each one, with the aim of producing a global perspective on the interpretation and clinical implications of the available data. The statements address issues that will be of relevance to all clinicians involved in prescribing adjuvant hormonal treatment for postmenopausal women with early breast cancer.

Consensus statements

1. The aim of adjuvant treatment is to reduce breast cancer mortality by reducing recurrence. When patients with breast cancer have an invasive recurrence, most will experience further disease progression resulting in reduced survival.

Reductions in recurrence rates historically have led to lower breast cancer mortality. Thus, the prevention of recurrence should be the initial goal of adjuvant endocrine therapy, especially from the point of view of the patient, and treatment decisions should initially be based on the ability of a particular agent to achieve this goal.

While the appearance of ductal carcinoma in situ or ipsilateral locoregional recurrence is not always followed by metastatic disease\(^8\)–\(^10\), for most patients even loco-regional recurrence is followed by disseminated disease or other progression, with a subsequent increase in mortality, compared with disease-free patients\(^10\)–\(^12\).

With successful adjuvant therapy, early breast cancer is potentially a curable condition. However, treatment for advanced disease is currently considered to be palliative, in that patients developing advanced breast cancer usually have limited survival. Therefore, the prevention of recurrence appears to be of paramount importance. The contrasting safety profiles of tamoxifen and the AIs are an important (but secondary) consideration, given the expected longer survival of patients with early disease compared with advanced disease.

2. AIs are superior to tamoxifen and are therefore the treatment of choice in oestrogen receptor (ER)-positive breast cancer. In newly diagnosed postmenopausal patients, AIs are considered the preferred therapy, and patients already receiving tamoxifen should consider switching to an AI.

In postmenopausal women, data from the ATAC trial\(^1\), and from the BIG 1-98 study\(^2\) show that anastrozole and letrozole, respectively, reduce breast cancer recurrence to a greater extent than tamoxifen when given as initial adjuvant endocrine therapy in postmenopausal women with hormone receptor-positive early breast cancer (Figure 1). Anastrozole treatment in ATAC reduced the risk of recurrence by 26% (hazard ratio [HR] = 0.74; 95% confidence interval [CI] 0.64–0.87; \(p = 0.0002\)) in patients with hormone receptor-positive disease compared with tamoxifen at 68 months of follow-up\(^1\). Further analysis of these data revealed that almost half of the excess recurrences in the tamoxifen group occurred during the first 2.5 years of therapy\(^1^3\), during the established initial ‘peak’ in recurrence following surgery\(^1^4\). Letrozole therapy in BIG 1-98 showed similar benefits to anastrozole, reducing the risk of recurrence by 28% compared with tamoxifen therapy at 26 months of follow-up (HR = 0.72; 95% CI 0.61–0.86; \(p < 0.001\))\(^2\). Together these results suggest an efficacy advantage for AIs compared with tamoxifen. Furthermore, current data from ATAC indicate that the treatment effect with anastrozole continues after cessation of therapy (the carry-over effect), in a similar way to that seen with tamoxifen\(^1\). Data comparing adjuvant exemestane treatment with tamoxifen...
will not be available until the first report from the Tamoxifen and Exemestane Adjuvant Multicentre (TEAM) trial. From the ATAC and BIG 1-98 trials, it can be concluded that both anastrozole and letrozole significantly reduce the risk of recurrence compared with tamoxifen as primary adjuvant endocrine therapy for women with hormone receptor-positive early breast cancer, and should therefore be offered to newly diagnosed patients as their initial treatment.

It is important to distinguish between switching strategy trials (where patients who have completed an initial period of tamoxifen treatment without recurrence are randomized to continue on tamoxifen or switch to an AI), and sequencing strategy trials (where patients are randomized before adjuvant treatment to receive either tamoxifen alone for 5 years, or a sequence of tamoxifen followed by an AI), as the resulting data relate to different patient populations. Switching study patient populations are by default enriched with patients who respond well to endocrine therapy by excluding patients who have had an early recurrence despite tamoxifen treatment. As such, switching and sequencing relate to different clinical decisions; switching is an issue pertaining to the best treatment for women already receiving adjuvant tamoxifen, and sequencing compares standard tamoxifen therapy alone

**Figure 1.** Kaplan-Meier curves showing (A) time to recurrence in the ATAC trial (hormone receptor-positive patients) (reproduced with permission from reference 1), and (B) disease-free survival in BIG 1-98 (all patients) (reproduced with permission from reference 2). HR = hazard ratio; CI = confidence intervals.
with an intended sequence of tamoxifen and an AI as adjuvant treatment for newly diagnosed women.

Data from several switching trials, including the ITA trial\(^1\), the IES\(^4\) and the combined analysis of ABCSG Trial 8 and ARNO 95\(^5\), indicate that switching to an AI from tamoxifen after 2–3 years of treatment is superior to continuing on tamoxifen for the full 5 years of therapy. In these trials, event-free survival was increased significantly in patients switched to an AI compared with those patients continuing on tamoxifen, by 65% with anastrozole in the ITA trial (HR = 0.35; 95% CI 0.20–0.63; \(p = 0.0002\)), 40% with anastrozole in the combined ABCSG Trial 8/ARNO 95 analysis (HR = 0.60; 95% CI 0.44–0.81; \(p = 0.0009\)) and by 32% in IES with exemestane (HR = 0.68; 95% CI 0.56–0.82; \(p < 0.001\)). Consequently, AIs appear to be the treatment of choice not only for newly diagnosed patients, but also for patients currently receiving tamoxifen as adjuvant therapy (Table 1).

### Table 1. Efficacy data from primary adjuvant, switched adjuvant and extended adjuvant trials, comparing adjuvant strategies involving aromatase inhibitors with 5 years of adjuvant tamoxifen

<table>
<thead>
<tr>
<th>Trial</th>
<th>AI Follow-up, months</th>
<th>Outcome measure*</th>
<th>HR vs. 5 years' T</th>
<th>95% CI, (p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary adjuvant therapy trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATAC</td>
<td>A</td>
<td>DFS</td>
<td>0.87</td>
<td>0.78–0.97, 0.01</td>
</tr>
<tr>
<td>BIG 1-98</td>
<td>L</td>
<td>DFS</td>
<td>0.81</td>
<td>0.70–0.93, 0.003</td>
</tr>
<tr>
<td>Switching trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IES</td>
<td>E</td>
<td>DFS</td>
<td>0.68</td>
<td>0.56–0.82, &lt; 0.001</td>
</tr>
<tr>
<td>ABCSG 8/ARNO 95</td>
<td>A</td>
<td>EFS</td>
<td>0.60</td>
<td>0.44–0.81, 0.0009</td>
</tr>
<tr>
<td>ITA</td>
<td>A</td>
<td>DFS</td>
<td>0.35</td>
<td>0.18–0.68, 0.001</td>
</tr>
<tr>
<td>Extended adjuvant therapy trials</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MA 17</td>
<td>L</td>
<td>DFS</td>
<td>0.58</td>
<td>0.45–0.76, &lt; 0.001</td>
</tr>
<tr>
<td>ABCSG 6a</td>
<td>A</td>
<td>EFS</td>
<td>0.64</td>
<td>0.41–0.99, 0.047</td>
</tr>
</tbody>
</table>

*Outcome measures may be defined differently for different trials

\(A\) = aromatase inhibitor; \(HR\) = hazard ratio; \(T\) = tamoxifen; \(CI\) = confidence intervals; \(ATAC\) = ‘Arimidex’, tamoxifen, alone or in combination; \(BIG\) = Breast International Group; \(IES\) = Intergroup Exemestane Study; \(ABCSG\) = Austrian Breast and Colorectal Cancer Study Group; \(ARNO\) = Arimidex-Nolvadex; \(ITA\) = Italian Tamoxifen Anastrozole; \(MA 17\) = National Cancer Institute of Canada trial; \(A\) = anastrozole; \(L\) = letrozole; \(E\) = exemestane; \(DFS\) = disease-free survival; \(EFS\) = event-free survival

3. As yet, there are no data from direct comparisons between a sequence of adjuvant endocrine therapy (i.e. tamoxifen followed by an AI) compared with 5 years of AI therapy alone. Data from ABCSG Trial 8 do not support a sequential treatment strategy, and indirect comparisons do not support a sequence of adjuvant therapy in preference to 5 years of AI therapy.

Until the publication of mature data from BIG 1-98, comparing 5 years of letrozole with tamoxifen-to-letrozole (and vice versa) sequenced treatment strategies, there are no available data comparing sequencing strategies with AI monotherapy. Preliminary analysis of data from ABCSG Trial 8 (median follow-up 54.6 months, \(n = 2926\)), which compared 5 years of tamoxifen with a sequence of tamoxifen followed by anastrozole after 2 years, revealed a trend for benefit in event-free survival for the sequence compared with tamoxifen monotherapy, but this was not statistically significant (HR = 0.76; \(p = 0.068\))\(^1\). However, when this analysis was repeated for the period starting 2 years after the initiation of therapy (i.e. from the time of the switch to anastrozole, in a similar way to current switching trials; \(n = 2529\)), a statistically significant benefit for anastrozole was apparent (HR = 0.63; \(p = 0.01\)), in agreement with data from the other switching trials. (Note that while the ABCSG Trial 8 was designed as a sequencing trial, its protocol allowed for its integration with ARNO 95 [a switching trial] to produce a combined switching analysis. Thus the ABCSG Trial 8/ARNO 95 combined analysis relates to switching, and ABCSG Trial 8 in isolation relates to sequencing.)

Comparisons of data from switching and initial adjuvant therapy strategies are difficult to make, as they contrast recurrence-free patients who have received 2–3 years of tamoxifen therapy with patients who have yet to receive any adjuvant endocrine therapy. The former population therefore excludes patients who recur early after surgery and do not respond well to adjuvant endocrine therapy, while the latter does not. Analysis of data from ABCSG Trial 8 illustrates the effect of patient selection in switching trials, suggesting that data obtained from switching trials overestimate the benefit of a treatment strategy that sequences tamoxifen to an AI. Enrichment of the study population may therefore contribute to the more favourable HR for recurrence (compared with 5 years of tamoxifen) for AIs from the various switching trials, compared with those from the initial adjuvant AI therapy studies\(^2\).

The suggestion that an initial period of tamoxifen treatment makes subsequent AI therapy more effective than would be the case if an AI were given to tamoxifen-naïve patients is therefore not supported by the available clinical data. In addition, there is no
satisfying biological explanation for such a ‘priming’ phenomenon.

In the absence of trial data comparing 5 years of AI with a sequencing strategy directly, the best we can do is to construct an indirect comparison using the available data. Such a model has already been described by Punglia et al., and indicated that a sequencing strategy provided modest benefits compared with adjuvant AI monotherapy. However, this model was limited in that it used a mix of endpoints from different trials (disease-free survival and time to recurrence), and assumed different carryover effects for tamoxifen and AIs. Furthermore, this model did not take fluctuating rates of recurrence into account.

Another recently published model of the available data provides an alternative explanation for the more favourable HR from switching trials compared with initial adjuvant trials. The ‘Deep’ model, constructed by Cuzick et al., incorporates the phenomenon of phenotypic receptor remodelling during tamoxifen therapy and predicts a consistent benefit in terms of recurrence for patients receiving primary AI therapy to at least 10 years of follow-up (Figure 2). Briefly, it has been suggested that a certain proportion of ER-positive/progesterone receptor (PgR)-positive tumours alter their receptor expression to ER-positive/PgR-negative during exposure to tamoxifen. Therefore, the phenomenon of altered receptor-expression may promote tamoxifen resistance and increase the likelihood of recurrence. In the context of comparisons between switching regimens and tamoxifen monotherapy, the impact of this process appears to be clear; switching to an AI may particularly benefit those patients whose micrometastases have altered receptor expression but whose disease has not yet recurred, while those continuing on tamoxifen are more likely to experience recurrence following receptor loss. Therefore, the enhanced HR values reported in the switching trials may not have been generated by an increased efficacy of the AI following initial tamoxifen, but due to the emergence of tamoxifen resistance on continued tamoxifen exposure, with the relative efficacy of the AI being unaffected. Furthermore, analysis of the Kaplan-Meier graph for recurrence in ATAC at 68 months of follow-up shows a widening of the gap between the plots for tamoxifen and anastrozole after about 30 months, which may indicate a worsening prognosis for those patients receiving tamoxifen whose tumours have undergone receptor remodelling during the first 30 months of treatment (Figure 1A).

Recent data from ABCSG Trial 8 and BIG 1-98 require the revision of these models. Firstly, the effect of the selected patient population in switching trials must be incorporated, which may be expected to increase the difference in recurrence rates between 5 years of AI treatment and a switched adjuvant therapy strategy. Secondly, there is preliminary evidence to suggest that the differential response of ER-positive/PgR-positive and ER-positive/PgR-negative tumours to AI therapy seen with anastrozole may not be applicable to letrozole, which appears to be more effective for ER-positive/PgR-positive tumours than ER-positive/PgR-negative tumours. Should the apparent discordance between these results (all of which were obtained in exploratory analyses) be confirmed, uncertainties would be raised as to how to use this information clinically and within the context of these models.

Overall, however, the main conclusion of the Cuzick model is unchanged; in terms of years lost to recurrence, a switching strategy is always inferior to 5 years of AI up to at least 10 years of follow-up. While all models are bound by the assumptions on which they are constructed, and necessitate improvement as new data are published, it appears that the effect of the excess

---

Figure 2. Kaplan-Meier estimates for incidence of recurrence with different adjuvant treatment strategies in the ‘Deep’ model (reproduced with permission from reference 18)
early recurrences (that occur with tamoxifen compared with an AI) on overall recurrence rate may not be fully balanced by a later switch to AI therapy. Of course, from the point of view of the patient, it may never possible to compensate for an early recurrence.

4. There may be advantages to continuing adjuvant therapy beyond 5 years. The optimal duration of adjuvant therapy with tamoxifen is 5 years, and this period has become standard for adjuvant endocrine therapy. However, the optimum treatment duration for primary AI therapy is not yet known. The optimum duration for AI use in patients previously treated with tamoxifen is unclear, but data currently show that there is a benefit for at least 2–3 years of AI treatment following 5 years of tamoxifen therapy.

The available data for extended adjuvant therapy show a clear benefit for continuing adjuvant therapy beyond 5 years of tamoxifen for both letrozole (compared with placebo) in the MA 17 trial, and anastrozole (compared with no further treatment) in ABCSG Trial 6a (Table 1). Although these trials studied different durations of extended adjuvant therapy, both concur that the rate of recurrence after 5 years of adjuvant tamoxifen therapy can be reduced. The standard 5-year adjuvant treatment period was adopted because the risks associated with greater than 5 years of tamoxifen outweigh its benefits. However, this period may not be optimal for AI therapy, and it is possible that shorter or longer periods of adjuvant therapy may be suitable for different patients, depending upon their specific disease characteristics. Further research is needed to define the optimum duration of adjuvant AI treatment.

5. There are no data which confirm that there is any group of patients for whom AIs are not effective adjuvant therapy.

Historically, the interpretation of subgroup analyses from adjuvant endocrine trials has brought about speculation as to the efficacy of AI therapy in certain patient populations. For example, in ATAC there was an early debate concerning reduced benefit compared with tamoxifen in patients who received chemotherapy. However, these concerns have become unfounded with further maturation of the data, and we may conclude that there are no subgroups of patients with hormone-responsive breast cancer for whom AIs are not at least as effective as tamoxifen. Subgroup analyses in general require careful interpretation, as they are liable to detect false treatment interactions as a result of smaller sample size compared with the main analysis; such treatment interactions may disappear with longer follow-up. Given the length of follow-up available for ATAC, it is now clear that there is no subgroup of patients who could not benefit from anastrozole as initial adjuvant therapy.

6. Reported gynaecological adverse events are substantially reduced with AIs compared with tamoxifen. The majority of gynaecological adverse events with tamoxifen occur during the first 2.5 years of treatment, and cause a burden to the patient that may affect compliance with therapy. Tamoxifen treatment may also lead to an increase in surgery for benign conditions.

It is well known that the oestrogen-agonist effect of tamoxifen on healthy endometrial tissue increases the incidence of gynaecological adverse events. In comparison with anastrozole, tamoxifen significantly increases the risk of endometrial cancer in patients receiving primary adjuvant endocrine therapy for breast cancer (incidence of endometrial cancer 0.8% and 0.2%, respectively, \( p = 0.02 \)). Lower rates of endometrial cancer have also been observed with patients receiving letrozole and exemestane, compared with tamoxifen, in the primary adjuvant and switched adjuvant settings, respectively.

Data from ATAC reveal significant increases in the incidence of benign gynaecological adverse events for tamoxifen-treated patients compared with those receiving anastrozole. Such events can be grouped into four categories: (1) endometrial thickening; (2) vaginal bleeding; (3) vaginal discharge; and (4) the appearance of endometrial polyps and fibroids. A recent analysis revealed that the majority of these events occur in the first 2.5 years of the 5-year adjuvant therapy period. The incidence of vaginal bleeding in women receiving tamoxifen has been reported to be approximately double that of women receiving an AI as primary adjuvant therapy (10.2% and 5.4% for tamoxifen and anastrozole in ATAC at 68 months of median follow-up \( p < 0.0001 \) and 6.6% and 3.3% for tamoxifen and letrozole in BIG 1-98 at 26 months of median follow-up \( p < 0.001 \), respectively). Where an AI is given after tamoxifen, the incidence of vaginal bleeding is also lower in the AI-treated group (5.5% and 4.0% for tamoxifen and exemestane, respectively, in IES at 31 months of median follow-up \( p = 0.05 \)).

An unavoidable consequence of an increase in gynaecological adverse events is an increase in gynaecological investigations to rule out malignancy. For instance, it may take up to 6 weeks and three investigations to rule out endometrial cancer following vaginal bleeding, although these figures are dependent upon local practice guidelines. Such investigations, while necessary, increase the treatment burden on patients and add the psychological stress of a possible
further cancer diagnosis to a patient already receiving treatment for breast cancer. Given that patients may experience several such episodes during the course of treatment, the consequences of gynaecological adverse events may be considerably greater than the physiological event itself. Furthermore, the occurrence of gynaecological adverse events may lead to an increased rate of prophylactic hysterectomy. In ATAC, there were almost four times as many hysterectomies carried out in the tamoxifen group than in the anastrozole group. Of the hysterectomies performed on tamoxifen-treated patients, 95 of 115 occurred as a result of benign diagnoses, compared with 23 of 30 hysterectomies in anastrozole-treated patients (Table 2). Therefore, adjuvant AI therapy may prevent not only gynaecological adverse events compared with tamoxifen, but also unnecessary surgery.

Gynaecological adverse events such as dyspareunia and vaginal dryness occur more often with AIs than tamoxifen and are of great concern to patients. However, such events are less likely to be related to malignancy than vaginal bleeding.

7. Bone problems with AIs are predictable and appear to be manageable.

Significantly increased fracture risks compared with tamoxifen have been demonstrated for anastrozole and letrozole in randomised trials of primary adjuvant therapy (11.0% and 7.7% for anastrozole at a median follow-up of 68 months; \( p < 0.0001 \)), (5.7% and 4.0% for letrozole at a median follow-up of 26 months; \( p < 0.001 \)), and result from an increase in bone turnover. Patients receiving AIs are therefore prone to loss of bone mineral density (BMD) and may be at risk of osteoporosis. In the MA 17 trial, following 5 years’ tamoxifen, patients receiving letrozole were significantly more likely to develop new osteoporosis than patients receiving placebo at a median follow-up of 30 months (8.1% and 6.0%, respectively; \( p = 0.003 \)).

Risk of bone fracture and osteoporosis naturally increases with age after the menopause. However, tamoxifen has known bone-protecting effects, and, as no direct comparison is available between AI-treated patients and a control population, it is difficult to estimate the extent to which AI therapy increases fracture risk over that which could be expected in untreated postmenopausal patients. It is possible, however, to predict which patients are at increased risk of osteoporosis and fracture by means of BMD monitoring via dual emission X-ray absorptiometry (DEXA) scanning. The American Society of Clinical Oncology (ASCO) has issued guidelines for the monitoring of bone health in patients with breast cancer, which include the use of bisphosphonates for the management of osteoporosis.

Analysis of data from ATAC reveals that the annual fracture rate for anastrozole treatment compared with tamoxifen therapy increases during the first 2 years of therapy, but then appears to stabilize during continued AI treatment and decreases on cessation of therapy to levels similar to those seen with tamoxifen (Figure 3). A diagnosis of osteoporosis is made when BMD has decreased by at least 10% compared with normal subjects. With the loss in BMD estimated at around 2% per year during the first 2 years of anastrozole therapy, a woman with normal BMD at treatment initiation is therefore unlikely to develop osteoporosis during 5 years of adjuvant therapy with an AI. Routine measurement of BMD prior to beginning adjuvant AI therapy would therefore identify which patients are at greatest risk of fracture and osteoporosis.

Adjuvant AI therapy is also associated with a significantly increased risk of musculoskeletal adverse events compared with tamoxifen therapy, as reported for ATAC at 68 months of follow-up (35.6% and 29.4% for anastrozole and tamoxifen, respectively; \( p < 0.0001 \)) and in BIG 1-98 at 26 months of follow-up (20.3% and 12.3% for letrozole and tamoxifen, respectively; \( p < 0.001 \)). The incidence of arthralgia in patients switching from tamoxifen to exemestane, and those receiving tamoxifen alone in IES (5.4% and 3.6%, respectively, at 31 months of follow-up), also shows an increase for patients switched to AI treatment, although this increase may have been ameliorated by initial exposure to tamoxifen.

The effect of the bisphosphonate zoledronic acid in postmenopausal women receiving adjuvant letrozole is currently being assessed in the Zometa/Femara Adjuvant Synergy Trial (Z-FAST). Preliminary findings at 6 months show that the total hip BMD in patients receiving upfront zoledronic acid was significantly higher than in patients receiving delayed zoledronic acid (difference = 2.42%; \( p < 0.001 \)). These data indicate that bisphosphonate therapy could be used successfully to manage the BMD of postmenopausal women receiving adjuvant AI treatment.

Table 2. Diagnoses leading to hysterectomy in the ATAC trial

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Patients, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Anastrozole</td>
</tr>
<tr>
<td></td>
<td>( n = 2229 )</td>
</tr>
<tr>
<td>Malignancy</td>
<td>7 (0.3)</td>
</tr>
<tr>
<td>Benign</td>
<td>23 (1.0)</td>
</tr>
<tr>
<td>Prolapse</td>
<td>7 (0.3)</td>
</tr>
<tr>
<td>Fibroids</td>
<td>8 (0.4)</td>
</tr>
<tr>
<td>Polyps</td>
<td>1 (&lt;0.1)</td>
</tr>
<tr>
<td>Ovarian cysts</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td>Other</td>
<td>5 (0.2)</td>
</tr>
</tbody>
</table>

© 2006 LIBRAPHARM LTD – Curr Med Res Opin 2006; 22(8)
Figure 3. Fracture risk during adjuvant therapy with tamoxifen and anastrozole in the ATAC trial. *Calculated using Kaplan-Meier estimates

The mechanisms by which AIs increase the incidence of arthralgia and joint symptoms are unknown, so current management of these conditions relies upon analgesics.

8. The risks of tamoxifen treatment with respect to deep-vein thrombosis (DVT), stroke and endometrial cancer are unpredictable in individual patients.

While it may be possible to monitor and predict the risk of fracture in patients treated with AIs, the same does not appear to be true for the risk of the most serious adverse events associated with tamoxifen, namely DVT, stroke and endometrial cancer. In the ATAC study, at a median follow-up of 68 months, the incidence of these events in anastrozole and tamoxifen-treated patients, respectively, were 1.6% and 2.4% (DVT; p = 0.02), 2.0% and 2.8% (ischaemic cerebrovascular event; p = 0.03) and 0.2% and 0.8% (endometrial cancer; p = 0.02). This issue constitutes a crucial difference between the management of patients receiving adjuvant endocrine therapy with tamoxifen and AIs.

There is some evidence to suggest that tamoxifen-associated thromboembolism is more likely to occur in women with the Leiden mutation in clotting Factor V, although further investigation is needed to define the size of this increased risk.

9. The relationship of coronary heart disease (CHD) to AI use requires further evaluation; there are no data relating to either tamoxifen or AIs in patients with pre-existing CHD. There is no evidence to contraindicate patients with CHD for AI therapy and CHD risk was not a factor for exclusion in any of the AI trials. Furthermore, current evidence suggests that AIs have either no or little effect on CHD and the presence of CHD should not impact on the prescribing of AIs for adjuvant use. Further follow-up is required to determine whether differences between the AIs exist.

The clinical significance of the comparative effects of tamoxifen and AIs on lipid profiles and risk of CHD is unclear. The Women’s Health Initiative trials evaluating hormone replacement therapy in postmenopausal women concluded that lipid profile changes under hormonal influence are not reliable predictors for events related to CHD. Therefore, the clinical significance of any lipid profile changes under the influence of tamoxifen or AIs remains uncertain.

Nevertheless, it is commonly considered that tamoxifen has a cardioprotective effect as a result of its significant lowering of total (p < 0.01) and low-density lipoprotein (p < 0.001) cholesterol. However, tamoxifen also significantly raises serum triglyceride levels (p < 0.001), which may counteract the effect of reduced cholesterol with respect to CHD risk. The Letrozole, Exemestane and Anastrozole Pharmacodynamics (LEAP) study recently compared the effect of these agents on lipid profile in healthy postmenopausal women. This small, comparative study revealed that differences exist between the different AIs in terms of their effects on lipid profiles, and that these effects fluctuate during treatment. After 24 weeks of treatment, there were few significant changes from baseline for letrozole and exemestane compared with anastrozole; for exemestane the ratio of low-density with high-density lipoprotein cholesterol was increased (p = 0.047), with an increased apolipoprotein B:A-I ratio (p = 0.023). Neither anastrozole nor letrozole produced any marked changes in these parameters, total cholesterol levels or triglyceride levels compared with baseline. Data from BIG 1-98 show no significant change in total cholesterol with letrozole treatment.

The most recent update of the Early Breast Cancer Trialists’ Collaborative Group (EBCTCG) meta-analysis
includes approximately 15,000 women treated with 5 years of tamoxifen or control over 15 years of follow-up, and found a trend towards a difference in cardiac deaths between women receiving adjuvant tamoxifen and control (120 and 132 deaths, respectively; \( p = 0.06 \))\(^{10} \). These data concur with a meta-analysis published in 2003\(^{4} \), which included > 52,000 patients from 32 trials who received tamoxifen in the adjuvant, preventative or advanced disease settings, or control therapy. At 5.6 years of follow-up, this meta-analysis found a significant reduction in relative risk (RR) for fatal myocardial infarctions (MI) of 0.62 in favour of tamoxifen (95% CI 0.41–0.93). However, with the exclusion of data from one particular trial, which had markedly different results from the others, the RR for fatal MI in favour of tamoxifen became non-significant (RR 0.81; 95% CI 0.48–1.37).

Conclusions regarding the relationship between AIs and cardiac risk are limited by the modest number of events reported currently. In ATAC at 68 months of follow-up, no significant difference was seen between anastrozole and tamoxifen in the incidence of MI (37 and 34 MIs in 3092 and 3094 patients for anastrozole and tamoxifen, respectively), cardiac death (49 and 46 cardiac deaths in 3092 and 3094 patients for anastrozole and tamoxifen, respectively)\(^{11} \) or ischaemic cardiovascular disease (4.1% and 3.4% for anastrozole and tamoxifen, respectively; \( p = 0.1 \))\(^{1} \). Thus, current evidence does not suggest an adverse effect on cardiac health with anastrozole. Presently, similar conclusions cannot be drawn for letrozole and exemestane until cardiac event data for these agents have been reported. In BIG 1-98, a significant increase in grade 3–5 cardiac events for letrozole compared with tamoxifen was seen at 26 months of follow-up (2.1% and 1.1%, respectively; \( p = 0.003 \)), although this result is based on few events\(^{2} \). In contrast, there were no significant differences in cardiovascular adverse events reported by the MA 17 trial of extended adjuvant letrozole versus placebo following 5 years of adjuvant tamoxifen therapy, after 2.5 years of follow-up\(^{10} \). In IES, with 37.4 months of follow-up, the incidence of MI was greater for patients receiving exemestane (20 and 8 MIs in 2352 and 2372 patients receiving exemestane and tamoxifen, respectively; \( p = 0.023 \)), but not cardiac death (13 and 12 cardiac deaths for patients receiving exemestane and tamoxifen, respectively).

Definitive assessment of the influence of letrozole and exemestane on CHD will require further study. None of the adjuvant AI trials used CHD as an exclusion criterion, and it is likely that any significantly increased cardiac risk with AIs compared with tamoxifen would have been detected in the current pool of data. Therefore, current evidence suggests that CHD risk should not influence the decision to prescribe an AI.

10. There is evidence that arterial vascular events (strokes) are increased with tamoxifen treatment, and that this increased risk requires patients to have their tamoxifen withdrawn for a suitable period prior to elective surgery. This may not be necessary with AI treatment.

Data from the National Surgical Adjuvant Breast and Bowel Project (NSABP)-P1 breast cancer prevention trial in healthy women receiving tamoxifen or placebo as breast cancer prophylaxis, show a trend towards increased relative risk of stroke with tamoxifen treatment compared with placebo (1.42 in favour of placebo; 95% CI 0.97–2.08; \( p = 0.1 \))\(^{4} \). Prophylactic tamoxifen for breast cancer is also associated with a significantly increased risk of developing a major venous thromboembolic event (odds ratio 2.1; 95% CI, 1.1–4.1)\(^{15} \). The impact of the increased risk of a venous thromboembolic event in patients receiving tamoxifen on the risks associated with elective surgery has yet to be quantified. Nevertheless, concomitant tamoxifen therapy should be taken into account by patients and physicians as a factor which may contribute to complications arising from elective surgery.

Data from ATAC at 68 months of follow-up show a significant decrease in the incidence of stroke in patients receiving anastrozole compared with those receiving tamoxifen (odds ratio 0.70; 95% CI 0.50–0.97; \( p = 0.03 \))\(^{1} \), although there is no available comparison between anastrozole therapy and placebo. The incidence of cerebrovascular accident or transient ischaemic attack was 1.0% in patients receiving either letrozole or tamoxifen in BIG 1-98 at 26 months of median follow-up\(^{2} \). Data for exemestane have yet to be published.

11. All future trials of adjuvant therapy should include tissue collection and storage as a standard procedure.

The research possibilities offered by the advent of translational research and genetic profiling mean it is essential that in future adjuvant trials, tissue samples are collected and stored to enable the future evaluation of any correlation between patient outcomes and genetic profiles. Such investigations may aid the assessment of risk and enable the tailoring of treatment to individual patients. The consent or otherwise of patients to the use of tissue for such purposes should be included at entry into future trials.

Conclusions

Current data confirm the superiority of AIs over tamoxifen for the adjuvant treatment of hormone
receptor-positive early breast cancer in postmenopausal women. Every treatment strategy investigated to date shows significant benefits associated with receiving an AI compared with tamoxifen. We can therefore conclude not only that newly diagnosed patients should receive an AI, but also that patients currently receiving adjuvant tamoxifen should consider switching to an AI.

A direct comparison of 5 years of AI therapy with switching from tamoxifen to an AI after 2-3 years is not yet available. Preliminary modelling of current data suggests that primary AI therapy is more effective than a switching regimen, and results in a lower rate of recurrence and fewer patient-years lost to recurrence over a follow-up of at least 10 years. However, to be resolved with more certainty, this issue requires further randomized trial data, which are expected to come from the BIG 1-98 study.

Serious gynaecological adverse events are more common with tamoxifen therapy than AI treatment. Such events not only lead to inconvenience and follow-up treatment for the patient, but also increase the likelihood of prophylactic surgery for benign conditions.

AI therapy is associated with increased bone turnover and BMD loss, with a consequent increase in fracture risk compared with tamoxifen treatment, which apparently disappears on cessation of AI therapy. However, the extent of this increased fracture risk compared with an untreated population is uncertain, as is the effect of the adjuvant treatment period on bone health in later life. Patients at high risk of fractures and osteoporosis can be monitored via DEXA scanning and managed where appropriate using bisphosphonate therapy. However, further trial data describing the whole of the treatment period are required to confirm this assertion. At this point it appears that musculoskeletal and bone adverse events with AI therapy are generally predictable and manageable.

Currently, there is no convincing evidence that AIs pose a risk to patients with respect to CHD or strokes. Further data are needed to identify the clinical significance of any differences in the effects of adjuvant endocrine therapies on lipid profiles.

Acknowledgements

Declaration of interest: This manuscript arose from a Breast Cancer Round Table meeting in Houston, Texas on 5–6 December 2005 supported by an unrestricted educational grant from AstraZeneca. The authors wish to thank Dr Martin Quinn from Complete Medical Communications, for providing medical writing support.

Members of the International Aromatase Inhibitor Expert Panel

Panel members of the Round Table meeting included:

Eric Lilfrange, University of Liège, Belgium; Sergio Simon, Hospital Israelita Albert Einstein, São Paulo, Brazil; Zhenzhou Shen, Fudan University, Shanghai Cancer Hospital, Shanghai, P.R. China; Tao Ouyang, Beijing Cancer Hospital, Beijing, P.R. China; Christian Jackisch, Department of Gynecology and Obstetrics Kilnikum Offenbach, Germany; Bernd Gerber, University of Rostock, Rostock, Germany; Paolo Pronzato, Ospedale S. Andrea, La Spezia, Italy; Paolo Marchetti, University of L’Aquila, L’Aquila, Italy and the Istituto Dermopatico Dell’Immacolata, Rome, Italy; Ana Lluch, Hospital Clinico Universitario, Valencia, Spain; Manuel Constenla, Complejo Hospitalario Pontevedra, Pontevedra, Spain; Tommy Fornander, Karolinska University Hospital, Stockholm, Sweden; Stig B. Holmberg, Sahlgrenska University Hospital, Gothenburg, Sweden; Richard Sainsbury, University College, London, UK; Mark Lansdown, Leeds Teaching Hospital NHS Trust, Leeds, UK; Giles Cunnick, High Wycombe Hospital, UK; Nihal Shah, Mount Vernon Centre for Cancer Treatment, Middlesex, UK; Xavier Pivot, Centre Hospitalier Universitaire de Besançon, University of Franche-Comte, France.

References

1. ATAC Trialists’ Group. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years’ adjuvant treatment for breast cancer. Lancet 2005;365:60-2
18. Cuzick J, Sasieni P, Howell A. Should aromatase inhibitors be used as initial adjuvant treatment or sequenced after tamoxifen? Br J Cancer 2006;94:460-4
42. Howell A, on behalf of the ATAC Trialists’ Group. ATAC trial update – authors’ reply. Lancet 2005;365:1225-6