Aromatase inhibitors for breast cancer: different structures, same effects?

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Abstract

Aromatase inhibitors (AIs) have become the first-choice endocrine drugs for postmenopausal breast cancer patients since they are associated with superior activity and better general tolerability when compared with tamoxifen both in the adjuvant and metastatic settings. As a consequence, the question is no more if a postmenopausal patient should have AIs as part of her adjuvant treatment, but when should it be started or which one should be preferentially used. Newer compounds, generally defined as third-generation AIs, are biochemically more selective and potent when compared with older ones, and they also show superior clinical activity. As yet, no large randomised study has been published comparing the three third-generation AIs on the market. Nevertheless, both laboratory and clinical data suggest that the steroidal (exemestane) and non-steroidal (anastrozole, letrozole) AIs may have slightly different toxicity profiles, probably due to the low androgenic action of the formers. While waiting for randomised data on clinical efficacy of third-generation AIs, such differences may help select the best drug in elderly patients with a low cumulative risk of relapse and a significant amount of co-morbidities, such as cardiovascular disease or osteoporosis.

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Introduction

More than 100 years of basic and clinical research on endocrine therapy has provided us with a complex armamentarium of drugs against breast cancer. The success of both ovariectomy (Beatson 1896) and adrenalectomy (Dao & Huggins 1955) was beyond the understanding and expectations of their proponents and opened the avenue of oestrogen deprivation as a means to block tumour growth. The selective efficacy of ovariectomy and adrenalectomy for respectively pre- and postmenopausal patients was the clue to understand that the main source of oestrogens is different according to the age of the patient. Conversely, the 1998 Oxford overview demonstrated that the selective oestrogen receptor modulator (SERM) tamoxifen was equally effective in the pre- and postmenopausal patients (Early Breast Cancer Trialists’ Collaborative Group 1998) and made it the drug of choice for all patients with endocrine-sensitive tumours, with the possible addition of ovarian ablation in premenopause.

It was only with the discovery aromatase inhibitors (AIs) that a real step forward was made possible (Santen et al. 1974), as until then no SERMS had provided superior activity when compared with tamoxifen. Therefore, the first report of the results of the Arimidex, tamoxifen alone or in combination trial (ATAC) by Michael Baum at the San Antonio Breast Cancer Symposium in 2001 represented a turning point in the history of breast cancer therapy (Baum et al. 2002). Since then, many other trials have reported their results, all of which confirm the superior activity and better general tolerability of AIs when compared with tamoxifen (Altundag & Ibrahim 2006). As a consequence, the question is no more if a postmenopausal patient should have AIs as part of her adjuvant treatment, but when should it be started (upfront, switch, extended strategies) or which one should be preferentially used.

Although no results from randomised trials comparing the third-generation AIs have yet been reported, interesting laboratory and clinical data are available...
suggested that some differences may exist, particularly between steroidal (exemestane) and non-steroidal (anastrozole, letrozole) AIs. In the absence of reliable comparative data on their efficacy, some differences such as those pertaining to the lipid profile or the bone mineral density (BMD) may help individualise the choice of the best AIs for each patient.

**Mechanism of action**

The AIs act through inhibition of the cytochrome P450 enzyme, aromatase, which catalyses the conversion of androgens to oestrogens. The steroidal or type I compounds are derivatives of androstenedione, which is the aromatase physiological substrate, while the non-steroidal or type II compounds are derived by phenobarbitone (like aminoglutethimide) or are characterised by the imidazole/triazole structure. Type I AIs bind covalently to the enzyme causing its irreversible inactivation, while the non-steroidal compounds are characterised by reversible binding. First-generation (testolactone, aminoglutethimide) and second-generation (formestane, fadrozole) compounds of both the classes are characterised by lower selectivity and potency when compared with the newer AIs (exemestane, anastrozole and letrozole; Hong & Chen 2006).

**Biochemical efficacy**

The efficacy of AIs may be assessed by measuring either the suppression of plasma oestrogens (indirect evidence of enzymatic aromatase activity) or the conversion of androgens into oestrogens (direct evidence of enzymatic activity). In vivo measurements of the biochemical efficacy of a compound depend on drug metabolism (half-life) and tissue distribution, and thus may significantly differ from what is seen in in vitro experiments (Geisler & Lønning 2005). A frequently cited example pertains to the second-generation compound, fadrozole, which in vitro revealed a higher biochemical efficacy when compared with third-generation letrozole, while in vivo showed a lower suppression of plasma oestrogens and also an inferior clinical activity (Tominaga et al. 2003).

Even among the third-generation AIs, significant differences have been reported in the time to reach steady state plasma levels or half-life and in the interaction with several cytochromes of the P450 superfamily. The latter, in particular, may exert important difference as far as drug–drug interactions are concerned (Buzdar et al. 2002).

Aromatase inhibition and oestradiol suppression show good correlation and are consistently higher for third-generation AIs when compared with first-generation and second-generation AIs. (Sainsbury 2004). Conversely, a recent randomised comparison of third-generation AI administered for 24 weeks in healthy women showed no significant difference in median percentual change from baseline for plasma concentrations of oestrone (E₁), oestradiol (E₂) and oestriol (E₃; Goss et al. 2007).

**Clinical efficacy in the advanced setting**

The relationship between the degree of oestrogen suppression and clinical outcome may be assessed by comparing either the prognosis of individuals exposed to the same drug or that of individuals exposed to different drugs. The former comparison has been attempted by few studies that revealed slightly better response rates with higher oestrogen suppression and also a marginal increase in plasma oestrogens at the time of relapse (see Lønning 2003 for a review).

Conversely, extensive data are available on the clinical efficacy of first-generation and second-generation compounds when compared with third-generation compounds in patients with advanced/metastatic breast cancer. Several studies have demonstrated that letrozole is associated with better response rates and time to progression when compared with aminoglutethimide or fadrozole (Bergh et al. 1997, Gershankovich et al. 1998, Rose et al. 2002, Tominaga et al. 2003). Accordingly, a meta-analysis comparing AIs versus standard hormonal therapy in advanced breast cancer showed that only third-generation AIs (hazard ratio (HR) = 0.87, 95% confidence interval (CI): 0.82–0.93; P < 0.001), but not first-generation and second-generation AIs (HR = 0.98, 95% CI: 0.90–1.07), are associated with a significant survival advantage (Mauri et al. 2006).

In summary, there is now a strong evidence of improved efficacy with third-generation AIs when compared with conventional therapies like megestrol acetate and tamoxifen, but also when compared with less potent AIs of the first-generation and second-generation classes. Conversely, the existence relationship between the different potency of third-generation AIs and clinical outcome has not been clearly proved.

**Clinical efficacy in the adjuvant and neoadjuvant settings**

The demonstration that third-generation AIs are superior to both megestrol acetate and tamoxifen in the advanced disease (see Altundag & Ibrahim 2006 for a review) led to the implementation of several large randomised trials in the adjuvant setting. Three types
of comparisons were performed against 5 years of
tamoxifen, which at that time was the standard
treatment for postmenopausal women with endocrine-
sensitive disease: 5 years of AIs (upfront strategy), 2–3
years of tamoxifen followed by 2–3 years of AIs
(switch strategy) and 5 years of AIs after 5 years of
tamoxifen (extended strategy).

All of the trials show superior disease-free survival
rates (Table 1; ATAC Trialists’ Group 2005, Goss et al.
2006, Coates et al. 2007, Coombes et al. 2007, Kaufmann
et al. 2007) for AIs when compared with tamoxifen, with
a relative risk reduction ranging from 17 to 44% and
absolute gains of 2.9 to 7.9%. Since patient populations
are different, no cross comparisons can be made between
different strategies or drugs. For instance, although lower
relative risk reductions are reported for the upfront when
compared with the switch and extended strategies,
patients in the former group of trials had a generally
less favourable prognosis. This may be at least partly
related to the selection of hormone-responsive patients
during the tamoxifen therapy and the exclusion of more
aggressive cases who were not randomised because they
had already experienced a relapse in the trials of switch
and extended therapy. On the other hand, upfront
treatment may prevent early recurrences (i.e. within
2–3 years from surgery) and thus accounts for a larger
absolute benefit, especially in patients with a more
aggressive disease.

A part from the recently reported ARimidex–
NOlvadex (ARNO) trial with anastrozole (Kaufmann
et al. 2007) and a meta-analysis of all trials adopting
the switch strategy with anastrozole (Jonat et al. 2006),
no other trial has reported a reduction in overall
mortality despite a considerable length of follow-up,
mainly because the number of events occurred has
been lower than expected. Nevertheless, subset
analyses have reported longer survivals for patients
with tumours expressing both oestrogen and pro-
gesterone receptors (ER+/PR+) treated with exem-
estane after 2–3 years of tamoxifen (Coombes et al.
2007) or with letrozole after 5 years of tamoxifen (Goss
et al. 2005) when compared with 5 years of tamoxifen
(Table 2).

When adopted as preoperative (neoadjuvant) treat-
ment, AIs consistently demonstrated greater efficacy
than tamoxifen with regard to breast conservation rate,
but not to clinical response rate, which was the primary
end point of all of these trials (Table 3; Ellis et al. 2001,
Semiglazov et al. 2005, Smith et al. 2005, Cataliotti
et al. 2006). Although differences in the clinical
efficacy of various AIs cannot be excluded, it is more
likely that differences in patient populations and
evaluation of tumour response may have accounted
for these inconsistent results.

In summary, prospective randomised data are required
to assess the clinical efficacy of third-generation AIs. The
MA 27 trial led by the National Cancer Institute of
Canada (NCIC) and the United States (US) Intergroup
comparing exemestane ± celecoxib with anastrozole ±
celecoxib in 6389 hormone receptor-positive postmeno-
pausal patients, and the Femara versus Anastrozole
Clinical Evaluation (FACE) trial comparing letrozole
versus anastrozole in 4000 postmenopausal, hormone
receptor- and node-positive patients, will provide
important answers within the next few years.

### Table 1 Efficacy of aromatase inhibitors (AIs) in the adjuvant setting: disease-free survival

<table>
<thead>
<tr>
<th>Treatment strategy</th>
<th>Protocol</th>
<th>FU (months)</th>
<th>Relative risk reduction (%)</th>
<th>Absolute risk reduction (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Upfront</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATAC</td>
<td>Ana versus Tam</td>
<td>68</td>
<td>17&lt;sup&gt;a&lt;/sup&gt;</td>
<td>3.7</td>
</tr>
<tr>
<td>BIG 1–98</td>
<td>Let versus Tam</td>
<td>51</td>
<td>18</td>
<td>2.9</td>
</tr>
<tr>
<td><strong>Sequential (switch)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IES</td>
<td>Tam→Exe versus Tam</td>
<td>55.7</td>
<td>26</td>
<td>3.4</td>
</tr>
<tr>
<td>ARNO</td>
<td>Tam→Ana versus Tam</td>
<td>30.1</td>
<td>34</td>
<td>4.2</td>
</tr>
<tr>
<td>ABCSG/ARNOb</td>
<td>Tam→Ana versus Tam</td>
<td>28</td>
<td>40</td>
<td>3.1</td>
</tr>
<tr>
<td>ITA</td>
<td>Tam→Ana versus Tam</td>
<td>64</td>
<td>44</td>
<td>7.9</td>
</tr>
<tr>
<td>Meta-analysis§</td>
<td>Tam→Ana versus Tam</td>
<td>30</td>
<td>41</td>
<td>3.0</td>
</tr>
<tr>
<td><strong>Extended adjuvant</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MA 17</td>
<td>Tam→Let versus Tam→placebo</td>
<td>30</td>
<td>42</td>
<td>4.6</td>
</tr>
</tbody>
</table>

FU, follow-up; ATAC, anastrozole, tamoxifen alone or in combination (ATAC Trialists’ Group 2005); BIG, breast International Group (Coates et al. 2007); IES, Intergroup Exemestane Study (Coombes et al. 2007); ARNO, ARimidex–NOlvadex (Kaufmann et al. 2007); ABCSG, Austrian Breast Cancer Study Group (Jakesz et al. 2005); ITA, Italian tamoxifen anastrozole (Boccardo et al. 2006); § (Jonat et al. 2006); MA 17, (Goss et al. 2005); Ana, anastrozole; Tam, tamoxifen; Let, letrozole; Exe, exemestane.

<sup>a</sup>ER+/PR+ or ER+/PR− subset.
<sup>b</sup>Event-free survival.
Clinical efficacy according to biological characteristics

The first study to hypothesise the existence of a differential activity of AIs versus tamoxifen according to the biological characteristics of tumour was a neoadjuvant comparison between tamoxifen and anastrozole for 4 months before surgery (Ellis et al. 2001). Patients with human epidermal growth factor receptor-1 (HER-1) and/or HER-2 overexpression had in fact a marked difference in the clinical response rates to letrozole versus tamoxifen (88 vs 21%; P < 0.001), suggesting that AIs may be more effective in some subset of patients.

In the adjuvant setting, a retrospective analysis of ATAC trial according to hormone receptor status suggested that although the time to recurrence was longer for anastrozole than tamoxifen in both the ER+ /PR+ and ER+ /PR− subgroups, the benefit was substantially greater in the PR− subgroup (Dowsett et al. 2005). Conversely, the MA 17 trial of extended therapy reported larger benefits for 5 years of letrozole after 5 years of tamoxifen in patients with ER+/PR− when compared with ER+/PR− tumours, implying greater activity of letrozole in tumours with a functional ER (Goss et al. 2005). Nevertheless, all other adjuvant studies of AIs do not support the hypothesis that PR status may help select the best hormonal treatment. (Table 4; Viale et al. 2007).

The reasons for these discordant results are unclear, but some light may be shed by a reanalysis of the prognostic and predictive ER and PR expression of the breast International Group (BIG) 1–98 study. The central review of pathological features changed the assessment of the locally evaluated receptor status in a substantial proportion of patients (Viale et al. 2007). In particular, while ~1% of local ER− patients were reclassified as ER+ at central review, the same figure

Table 2 Efficacy of aromatase inhibitors (AIs) in the adjuvant setting: overall survival

<table>
<thead>
<tr>
<th>Treatment strategy</th>
<th>Protocol</th>
<th>FU (months)</th>
<th>Relative risk reduction (%)</th>
<th>P level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Upfront</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ATAC</td>
<td>Ana versus Tam</td>
<td>68</td>
<td>3a</td>
<td>0.7</td>
</tr>
<tr>
<td>BIG 1–98</td>
<td>Let versus Tam</td>
<td>51</td>
<td>9</td>
<td>0.35</td>
</tr>
<tr>
<td><strong>Sequential (switch)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IES</td>
<td>Tam→Exe versus Tam</td>
<td>55.7</td>
<td>15/17b</td>
<td>0.08/0.05b</td>
</tr>
<tr>
<td>ARNO</td>
<td>Tam→Ana versus Tam</td>
<td>30.1</td>
<td>47</td>
<td>0.04</td>
</tr>
<tr>
<td>ABCSG/ARNO</td>
<td>Tam→Ana versus Tam</td>
<td>28</td>
<td>1</td>
<td>0.16</td>
</tr>
<tr>
<td>ITA</td>
<td>Tam→Ana versus Tam</td>
<td>64</td>
<td>44</td>
<td>0.1</td>
</tr>
<tr>
<td>Meta-analysis§</td>
<td>Tam→Ana versus Tam</td>
<td>30</td>
<td>29</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Extended adjuvant</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MA 17</td>
<td>Tam→Let versus Tam→placebo</td>
<td>30</td>
<td>18/42c</td>
<td>0.3/NAc</td>
</tr>
</tbody>
</table>

FU, follow-up; ATAC, anastrozole, tamoxifen alone or in combination (ATAC Trialists’ Group 2005); BIG, breast International Group (Coates et al. 2007); IES, Intergroup Exemestane Study (Coombes et al. 2007); ARNO, ARimidex–NOlvadex (Kaufmann et al. 2007); ABCSG, Austrian Breast Cancer Study Group (Jakesz et al. 2005); ITA, Italian tamoxifen anastrozole (Boccardo et al. 2006); §(Jonat et al. 2006); MA 17, (Goss et al. 2005); Ana, anastrozole; Tam, tamoxifen; Let, letrozole; Exe, exemestane; NA, not available.
aEvent-free survival.
bER+/unknown subset.
cER+ and PR+ subset, 95% CI: 0.37–0.90.

Table 3 Summary of neoadjuvant aromatase inhibitors (AIs) trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Duration</th>
<th>Trial arms (n)</th>
<th>CRR (%)</th>
<th>P value</th>
<th>BCS (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMPACT</td>
<td>3 months</td>
<td>Ana (113)</td>
<td>37.0</td>
<td>0.87</td>
<td>46.0</td>
<td>0.03*</td>
</tr>
<tr>
<td>PROACT</td>
<td>3 months</td>
<td>Ana (228)</td>
<td>39.5</td>
<td>0.29</td>
<td>30.8</td>
<td>0.04**</td>
</tr>
<tr>
<td>Ellis et al. (2001)</td>
<td>4 months</td>
<td>Let (154)</td>
<td>55.0</td>
<td>&lt;0.001</td>
<td>45.0</td>
<td>0.022</td>
</tr>
<tr>
<td>Semiglazov et al. (2005)</td>
<td>3 months</td>
<td>Exe (76)</td>
<td>76.3</td>
<td>0.05</td>
<td>36.8</td>
<td>0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Tam (75)</td>
<td>36.8</td>
<td></td>
<td>20.0</td>
<td></td>
</tr>
</tbody>
</table>

CRR, clinical response rate; BCS, breast-conserving surgery; Ana, anastrozole; Tam, tamoxifen; Let, letrozole; Exe, exemestane; IMPACT, Immediate Preoperative Anastrozole, tamoxifen or Combined with tamoxifen (Smith et al. 2005); PROACT, Preoperative Arimidex compared with tamoxifen (Cataliotti et al. 2006).
was substantially higher for the PR (16%). Since central assessment also provided better prediction of patients’ outcome, it is likely that the results from other studies may have biased by local interpretation of hormone expression. In accordance with this hypothesis, a recent reanalysis of the ATAC data with central review of hormone receptor expression did not confirm the initial results of a selective advantage of AIs for patients with ER$^C$/PR$^C$tumours (Dowsett et al. 2006).

### Lack of cross-resistance

The first demonstration of the lack of cross-resistance between different AIs was reported in advanced breast cancer patients who showed clinical response to formestane after progression on aminoglutethimide (Murray & Pitt 1995). In a seminal study, Lønning et al. (2000) measured the clinical efficacy and the effect on serum E$_2$, oestrone and oestrone sulphate levels of exemestane in patients previously treated with aminoglutethimide or other non-steroidal AIs. After 8 weeks of exemestane, the overall response rate was 8.1% in patients previously treated with aminoglutethimide and 4.8% in those treated with other non-steroidal AIs. Exemestane following aminoglutethimide was associated with enhanced aromatase inhibition, while no difference in any type of serum oestrogen was associated with the switch from other ns-AIs to exemestane. Therefore, the authors were able to conclude that objective response or durable stable disease achieved by exemestane after ns-AIs could not be explained by enhanced aromatase inhibition.

Several publications have addressed this issue, showing that significant benefit can be achieved with exemestane after second-generation and third-generation non-steroidal AIs (Table 5; Geisler et al. 1996, Thürlimann et al. 1997, HarperWynne & Coombes 1999, Carlini et al. 2001, 2007, Bertelli et al. 2005, Iaffaioli et al. 2005, Steele et al. 2006). Furthermore, partial non-cross-resistance between steroidal and non-steroidal AIs may be independent of the sequence employed, according to the results of a small study of sequential treatment with exemestane and non-steroidal AIs in advanced breast cancer (Bertelli et al. 2005).

Current explanations to the partial lack of cross-resistance take into consideration either differences in intra-tumour pharmacology (i.e. effects on breast cancer aromatase) or tissue pharmacokinetics, or additional endocrine effects of the steroidal aromatase inactivators (i.e. weak androgenic activity of its 17-hydroxyexemestane metabolite; Lønning 2003).

### Side effects: cardiovascular diseases

The comparison of all types of vascular events in the adjuvant trials of AIs versus tamoxifen clearly shows that AIs are associated with a consistently lower risk of thrombotic events. The ATAC (ATAC Trialists’ Group 2005) and ARNO (Kaufmann et al. 2007) trials also report a significantly lower risk of cerebrovascular events with anastrozole, although the numbers are small (Table 6).

The publication of the BIG 1–98 trial captured the attention on the potential detrimental effect of letrozole on the incidence of cardiovascular events. Although no significant overall difference was reported in the incidence of heart failure and ischemic heart disease, there was a significant excess of severe events (grades 3–5) of both types with letrozole when compared with tamoxifen (Coates et al. 2007). Accordingly, letrozole was also associated with a significant excess of other cardiovascular disorder not otherwise specified (Table 6).

The potential negative effect of letrozole on cardiovascular diseases reported in the upfront adjuvant BIG 1–98 study (Coates et al. 2007) has been

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**Table 4** Comparison of hazard ratios for disease-free survival from clinical trials of aromatase inhibitors (AIs) according to ER and PR status

<table>
<thead>
<tr>
<th></th>
<th>ER$^+$/PR$^+$</th>
<th></th>
<th></th>
<th>ER$^+$/PR$^-$</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% of all pts</td>
<td>HR</td>
<td>95% CI</td>
<td>% of all pts</td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>ATAC</td>
<td>61</td>
<td>0.84</td>
<td>0.69–1.02</td>
<td>15</td>
<td>0.43</td>
<td>0.31–0.61</td>
</tr>
<tr>
<td>ABSAG/ARNO</td>
<td>78</td>
<td>0.66</td>
<td>0.46–0.93</td>
<td>18</td>
<td>0.42</td>
<td>0.19–0.92</td>
</tr>
<tr>
<td>IES</td>
<td>55</td>
<td>0.66</td>
<td>0.51–0.87</td>
<td>15</td>
<td>0.58</td>
<td>0.38–0.90</td>
</tr>
<tr>
<td>BIG 1–98</td>
<td>85</td>
<td>0.70</td>
<td>0.57–0.85</td>
<td>10</td>
<td>0.84</td>
<td>0.54–1.31</td>
</tr>
<tr>
<td>MA 17</td>
<td>73</td>
<td>0.49</td>
<td>0.36–0.67</td>
<td>12</td>
<td>1.21</td>
<td>0.63–2.34</td>
</tr>
</tbody>
</table>

ER, oestrogen receptor; PR, progesterone receptor; Pts, patients; HR, hazard ratio; CI, confidence interval; ATAC, anastrozole, tamoxifen alone or in combination (Dowsett et al. 2005); ABSAG/ARNO, Austrian Breast Cancer Study Group/ARimidex–NOlvadex (Jakesz et al. 2005); BIG, breast International Group (Viale et al. 2007); IES, Intergroup Exemestane Study (Coombes et al. 2007); ITA, Italian tamoxifen anastrozole (Boccardo et al. 2006); MA17, (Goss et al. 2005).
attributed to the lack of the protective effect of tamoxifen rather than to a true toxicity of the drug. Nevertheless, this explanation is likely unfounded since tamoxifen is not actually associated with beneficial or adverse cardiovascular effects in the NSABP-P1 chemoprevention trial (Fisher et al. 2001) and in a meta-analysis of all adjuvant trials (Braithwaite et al. 2003).

Conversely, some interesting insights may be derived by looking at the change in lipid profiles by the type of AIs. By comparing all AIs versus tamoxifen trials, it appears that both anastrozole (ATAC Trialists’ Group 2005) and letrozole (Coates et al. 2007) are associated with a significant increase in low-grade hypercholesterolaemia, whereas exemestane is not (Coombes et al. 2007). A differential effect on the lipid profile of steroidal versus non-steroidal AIs had already been suggested by Goss et al. (2004a,b) who showed that 16 weeks of treatment with exemestane in ovariectomised rats significantly prevented the increase in serum cholesterol and low-density lipoprotein levels, while this protective effect was not seen with letrozole. More recently, a comparison of the effect of exemestane versus tamoxifen on the lipid profile of postmenopausal early breast cancer patients was reported in the preliminary results of the TEAM Greek sub-study at 12 months of follow-up. Although, mean LDL levels were higher in the exemestane versus the tamoxifen arm, triglyceride levels were lower, while no difference was reported in total cholesterol.

Table 5 Studies evaluating different aromatase inhibitors and inactivators sequentially

<table>
<thead>
<tr>
<th>Author</th>
<th>Comparison</th>
<th>CR + PR/total (%)</th>
<th>CB/total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murray &amp; Pitt (1995)</td>
<td>AG → formestane</td>
<td>23/112 (20.5)</td>
<td>48/112 (42.8)</td>
</tr>
<tr>
<td>Geisler et al. (1996)</td>
<td>AG → formestane</td>
<td>2/10 (20.0)</td>
<td>2/10 (50.0)</td>
</tr>
<tr>
<td>Thürlimann et al. (1997)</td>
<td>AG → exemestane</td>
<td>20/78 (25.6)</td>
<td>47/78 (60.2)</td>
</tr>
<tr>
<td>Lønning et al. (2000)</td>
<td>AG → exemestane</td>
<td>11/136 (8.0)</td>
<td>37/136 (27.2)</td>
</tr>
<tr>
<td>Lønning et al. (2000)</td>
<td>Anastrozole/letrozole → exemestane</td>
<td>5/105 (4.8)</td>
<td>21/105 (20.0)</td>
</tr>
<tr>
<td>HarperWynne &amp; Coombes (1999)</td>
<td>Formestane → exemestane</td>
<td>2/21 (9.5)</td>
<td>12/21 (57.1)</td>
</tr>
<tr>
<td>Carlini et al. (2001)</td>
<td>Anastrozole/letrozole → formestane</td>
<td>0/20 (0)</td>
<td>11/20 (55.0)</td>
</tr>
<tr>
<td>Iaffaioli et al. (2005)</td>
<td>Anastrozole → exemestane</td>
<td>4/50 (8.0)</td>
<td>22/50 (44.0)</td>
</tr>
<tr>
<td>Bertelli et al. (2005)</td>
<td>Anastrozole/letrozole → exemestane</td>
<td>2/23 (8.7)</td>
<td>10/23 (43.5)</td>
</tr>
<tr>
<td>Steele et al. (2006)</td>
<td>Anastrozole/letrozole → exemestane</td>
<td>6/108 (5.0)</td>
<td>50/108 (46.0)</td>
</tr>
<tr>
<td>Carlini et al. (2007)</td>
<td>Anastrozole/letrozole → exemestane</td>
<td>1/30 (3.3)</td>
<td>14/30 (46.6)</td>
</tr>
<tr>
<td>Chin et al. (2007)</td>
<td>Anastrozole/letrozole → exemestane</td>
<td>6/31 (19.4)</td>
<td>17/31 (55.0)</td>
</tr>
</tbody>
</table>

AG, aminoglutethimide; CR, complete response; PR, partial response; CB, clinical benefit.

Table 6 Vascular events in Aromatase inhibitors (AIs) versus tamoxifen trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Median FU (months)</th>
<th>CV event definition</th>
<th>Cardiovascular events (%)</th>
<th>P</th>
<th>Thrombotic events (%)</th>
<th>P</th>
<th>Cerebrovascular events (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATAC</td>
<td>68</td>
<td>IHD</td>
<td>4.1 vs 3.4</td>
<td>0.1</td>
<td>2.8 vs 4.5</td>
<td>0.0004</td>
<td>2.0 vs 2.8</td>
<td>0.03</td>
</tr>
<tr>
<td>BIG 1–98</td>
<td>51</td>
<td>All</td>
<td>5.5 vs 5.0</td>
<td>0.48</td>
<td>2.0 vs 3.8</td>
<td>0.001</td>
<td>1.0 vs 1.0</td>
<td>0.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HF</td>
<td>1.0 vs 0.6</td>
<td>0.14*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>IHD</td>
<td>2.2 vs 1.7</td>
<td>0.21*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other</td>
<td>0.8 vs 0.2</td>
<td>&lt; 0.01</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IES</td>
<td>55.7</td>
<td>All IHD</td>
<td>9.9 vs 8.6</td>
<td>0.12</td>
<td>1.9 vs 3.1</td>
<td>0.001</td>
<td>2.5 vs 2.4</td>
<td>0.89</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MI</td>
<td>1.3 vs 0.8</td>
<td>0.08</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HF</td>
<td>1.8 vs 1.8</td>
<td>0.94</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Other</td>
<td>11.3 vs 11.2</td>
<td>0.96</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ARNO/ABSCG</td>
<td>28</td>
<td>MI</td>
<td>&lt;1 vs &lt;1</td>
<td>1</td>
<td>&lt;1 vs &lt;1</td>
<td>0.034</td>
<td>&lt;1 vs &lt;1</td>
<td>0.064</td>
</tr>
<tr>
<td>ITA</td>
<td>64</td>
<td>All CVD</td>
<td>7.6 vs 6.2</td>
<td>0.6</td>
<td>2.2 vs 4.4</td>
<td>0.2</td>
<td>NI</td>
<td></td>
</tr>
<tr>
<td>MA 17b</td>
<td>28.8</td>
<td>All</td>
<td>4.1 vs 3.6</td>
<td>0.4</td>
<td>0.2 vs 0.4</td>
<td>0.06</td>
<td>0.6 vs 07</td>
<td>NS</td>
</tr>
</tbody>
</table>

AI, aromatase inhibitor; T, tamoxifen; PI, placebo; IHD, ischemic heart disease; MI, myocardial infarction; HF, heart failure; NS, not significant; NI, not included in mature data; ATAC, anastrozole, tamoxifen alone or in combination (ATAC Trialists’ Group 2005); BIG, breast International Group (Coates et al. 2007); IES, Intergroup Exemestane Study (Coombes et al. 2007); ABCSG/ARNO, Austrian Breast Cancer Study Group/ARimidex–NOlvadex (Jakesz et al. 2005); ITA, Italian tamoxifen anastrozole (Boccardo et al. 2006); MA 17, (Goss et al. 2005). *P = 0.001 for grade 3–5 events.

Other cardiovascular events included cardiovascular disorder not otherwise specified.

Versus placebo.
and HDL levels, supporting the clinical data that the two drugs may exert a similar action on cardiovascular risk (Markopoulos et al. 2005).

In summary, AIs are associated with lower thrombotic risk when compared with tamoxifen, while the suggestion of a possible unfavourable balance of AIs on cardiovascular risk needs to be confirmed. In particular, this concern may not apply to exemestane that may actually decrease triglyceride levels when compared with tamoxifen, whose supposed cardiac benefits have probably been overemphasised in the past.

**Side effects: osteoporosis**

The osteoporotic risk of a woman is closely related to her age at menopause since oestrogen deprivation is a main factor in determining bone loss. In postmenopausal women, body mass index is inversely related to the risk of osteoporosis since most of the conversion of androgens into oestrogens by the aromatase enzyme occurs in the fat tissue. Aromatisation is the main source of oestrogens in menopause, and thus it is expected that all AIs decrease BMD when compared with placebo, and to a higher extent when compared with tamoxifen that lowers the osteoporotic risk due to its well-known oestrogenic properties on the bone (McCloskey 2006).

Indeed, significant bone loss is reported in all studies during AIs use when compared with tamoxifen or placebo, but it appears somewhat lower with steroidal versus non-steroidal AIs. AIs are also associated with higher fracture rates than tamoxifen in most studies, including the Intergroup Exemestane Study (IES) trial with exemestane (Coombes et al. 2007). Conversely, it appears that 5 years of tamoxifen followed by letrozole may partly protect bones from the detrimental action of AIs, as demonstrated by the MA 17 trial (Goss et al. 2005) that showed no difference in the clinical fracture rate, despite a significant change in the BMD versus placebo (see Chien & Goss 2006 for a review).

The clinical effect of different AIs on the bone can be assessed quantitatively by the annual fracture rate per 1000 women-years. An indirect comparison among third-generation AIs shows that exemestane is associated with less fractures (19.2) when compared with anastrozole and letrozole (21.6 and 22.0 respectively; ATAC Trialists’ Group 2005, Coates et al. 2007, Coombes et al. 2007). A more favourable effect of steroidal AI on the bone is also suggested by animal laboratory data. Exemestane decreases overall bone turnover and prevents bone loss at the lumbar vertebrae and whole femora in ovariectomised rats (Geisler et al. 2006), while these protective effects are not seen with the non-steroidal AI letrozole (Goss et al. 2004a,b).

A possible explanation of this differential effect of exemestane on the bone takes into account its androgenic activity that may exert a stimulatory action on bone formation. In a randomised, placebo-controlled study of postmenopausal women with early breast cancer, the decrease in BMD with exemestane when compared with placebo was partially reversed during a 1-year follow-up (Geisler et al. 2006). Accordingly, in the exemestane arm of the IES randomised study, arm resorption marker measurements were the highest at 12 months and then decreased, while bone formation markers peaked between 18 and 24 months (Coleman et al. 2007). The effects of 24 months of treatment with exemestane, anastrozole or letrozole on the serum and urine levels of biomarkers of bone turnover were recently compared in 84 healthy postmenopausal women. Bone resorption markers like N-terminal telopeptide were increased to the greatest extent by letrozole, while exemestane was associated with increased serum levels of the bone formation marker like serum procollagen type I N-terminal propeptide, suggesting a specific bone formation effect related to its androgenic structure (Goss et al. 2007).

**Conclusions**

The efficacy of third-generation AIs has not been directly compared in double-blind, randomised controlled trials, making selection difficult for clinicians. Although large differences in efficacy are unlikely to exist, data from direct comparisons are eagerly awaited and will provide crucial information. It is currently unknown whether differences in potency or biochemical structure of third-generation AIs will translate into differences in clinical efficacy. Nevertheless, both laboratory and clinical data suggest that the steroidal and non-steroidal AIs may have slightly different toxicity profiles, probably due to the low androgenic action of the former drugs. Note that the toxicity profile is particularly relevant for elderly patients with a low cumulative risk of relapse and a significant amount of co-morbidities, such as cardiovascular disease or osteoporosis. Since these patients deserve very well-balanced therapeutic decisions according to the principle of primum non nocere, their best bet may well be the less toxic and not the most potent of these drugs.
Acknowledgment

The authors declare that there is no conflict of interest that would prejudice the impartiality of this scientific work.

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