

Long-term safety of aromatase inhibitors in the treatment of breast cancer

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Abstract: Following promising data for metastatic breast cancer in terms of efficacy and safety profile, third-generation aromatase inhibitors (AI), anastrozole, letrozole, and exemestane, underwent a full development in early setting. If recent results consistently show the superiority of these agents over tamoxifen, the therapeutic strategies of AIs in adjuvant setting are still debated. Beyond the choice of clinical strategy, the long duration of exposure to AI in adjuvant setting required a full determination of the long-term toxicity profile of these agents. While all three AIs have either favorable (decreased incidence of hot flashes, gynecologic and thromboembolic side-effects) or unfavorable (skeletal complications, arthralgia, musculoskeletal pain, sexual dysfunction) class adverse events, some variability between AIs has been reported in side-effects as well as gastrointestinal, urogenital, neurologic, and visual disturbances, confirming the lack of interchangeability between the three AIs. The overall therapeutic index of AIs appears today superior to that of tamoxifen with proven improved efficacy and better toxicity profile. This review will explore the results from the available adjuvant AIs trials with a particular emphasis on safety profiles, quality of life, and therapeutic index, helping to define the present role of AIs in the adjuvant management of postmenopausal patients with breast cancer.

Keywords: breast cancer, aromatase inhibitors, adjuvant, safety profile

Introduction

Breast cancer is the most common cancer in women, with a worldwide yearly estimate of more than 1.1 million new cases of invasive breast cancer and more than 400,000 deaths per year, in keeping with a high prevalence (more than 4.0 million survivors up to 5 years following diagnosis) (Parkin et al 2005). Early mammography screening programs and important therapeutic advances in the treatment of early (EBCTCG 2005) and metastatic disease (André et al 2004) are thought to be the most important factors explaining this high prevalence.

In general, the treatment for patients with hormone-sensitive early breast cancer involves removal of the tumor by surgical and/or radiolotherapeutic techniques, followed by adjuvant endocrine therapy. Most patients will be treated with endocrine therapy postoperatively, since the use of adjuvant therapy significantly reduces the risks of tumor recurrence (EBCTCG 2005). In addition to endocrine therapies, adjuvant treatment may include chemotherapy, which has also been shown to increase survival (EBCTCG 2005).

When considering breast cancer carcinogenesis and therapeutic targeting, estrogens and oestrogen receptors are among the most relevant prognostic and predictive factors (Colozza et al 2005). Lifetime cumulative exposure to oestrogen and elevated levels of plasma oestrogen are correlated with the risk of developing breast cancer (EHBCCG 2002), and the oestrogen receptor (ER) is increasingly expressed as normal epithelium progresses to hyperplasia, hyperplasia with atypia, and finally ductal carcinoma in situ

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(Allred et al 2001). Therefore, antagonizing oestrogen is a logical approach to the treatment and prevention of breast cancer.

Over 100 years ago, Beatson removed the ovaries of a premenopausal woman with advanced breast cancer, achieving a treatment response of 42 months' duration and demonstrating, for the first time, the value of estrogen withdrawal in the management of breast cancer (Beatson 1896). Contemporary endocrine therapy was introduced to the clinic over 30 years ago. Subsequent investigation has, in the main, concentrated on providing additional endocrine methods of depriving tumor cells of estrogen stimulation or targeting the estrogen receptor (ER). The selective oestrogen receptor modulator (SERM), tamoxifen, has been for many years the standard adjuvant endocrine treatment for postmenopausal women with ER+ve and/or PgR+ve disease. However, tamoxifen was shown to be associated with side-effects, sometimes potentially life-threatening, due to its partial oestrogen agonist activity; these side-effects include an increased incidence of endometrial cancer (Wysowski et al 2002; EBCTCG 2005) and thromboembolic events (Fisher et al 1996) with an incidence related to the drug exposure duration. The facts that many advanced ER+ve tumors fail to respond to tamoxifen, and those that do respond ultimately acquire tamoxifen resistance, pleaded in favor of alternative endocrine therapies (Ring and Dowsett 2004). All these observations for tamoxifen led to the search of new anti-hormonal agents with improved therapeutic ratios.

The first two generations of aromatase inhibitors (AIs) were introduced in the treatment of metastatic disease but, mostly related to an unfavorable therapeutic index compared to tamoxifen, did not reach the adjuvant setting (Segalof et al 1962). More recently, third-generation AIs (anastrozole, letrozole, and exemestane) showed, for postmenopausal women with advanced disease, superiority over other hormonal agents, including megestrol acetate and most importantly tamoxifen (Buzdar et al 2002). These three endocrine agents were subsequently studied extensively in early breast cancer. In this article, we will review the efficacy and safety data of long-term use of AIs for the adjuvant treatment of postmenopausal patients with endocrine sensitive breast cancer.

Mechanism of action and pharmacology

In postmenopausal women, the AIs block the P450 cytochrome enzyme aromatase, responsible for the conversion

of androgens to estrogens via a pathway which is the main source of oestrogen, consequently suppressing oestrogen levels. In postmenopausal population, estrogens are produced in the adrenal glands, the skin, the muscles, and the adipose tissue (Miller and Dixon 2002). Additionally, a majority of breast tumors demonstrate the presence of intra-tumor aromatase activity, a likely source of local oestrogen for the tumor cells (Bolufer et al 1992).

In contrast, for premenopausal women, AIs induce an increase in gonadotropin secretion secondary to the reduced negative feedback of oestrogen to the pituitary. The consequence is ovarian stimulation and a potential increase in ovarian size which may result in ovarian cysts, thereby confirming the absence of indication of AI treatment in premenopausal patients.

AIs were first developed as a non-surgical means to reduce estrogen production in patients with hormone-responsive tumors. The first-generation AI, aminoglutethimide, an inhibitor of adrenal steroidogenesis, was studied almost 30 years ago. However, although significantly suppressing estrogen production, this agent was non-specific, altering as a consequence several intra-adrenal enzyme pathways, and producing sedative side-effects at the level of the central nervous system (Samojlik et al 1980; Perez and Borja 1992). Subsequently, so-called 'second-generation' AIs, such as 4-hydroxyandrostenedione (formestane) and fadrozole (CGS 16,949A), were found to be significantly more potent and better tolerated than aminoglutethimide. However, they did not show any benefit over tamoxifen (Wiseman and McTavish 1993).

Subsequently, in the late 1980s and early 1990s, research focused on developing agents with increased potency and higher selectivity. The identification of two different mechanisms of aromatase inhibition led to the development of two types of third-generation AIs. Type I aromatase inhibitors are androgen analogues, which interfere with the substrate-binding site of the enzyme and blocking the enzymatic complex by producing an unbreakable covalent bond between the inhibitor and the enzyme protein (they are also called aromatase inactivators). Exemestane is the only aromatase inactivator available as endocrine therapy.

Nonsteroidal type II AIs block the electron transfer chain by the cytochrome P450 prosthetic group of the aromatase complex, acting as competitive inhibitors reversibly bound to the active enzymatic site. There are two type II AIs in clinical practice: anastrozole and letrozole.

Secondary to a good bioavailability, all AIs used in the clinic are given orally, once daily. The time duration needed

to reach maximal estrogen suppression ranges from 2 to 7 days. The half-lives are quite different between the various AIs: respectively 41 and 27 hours for anastrozole and exemestane but longer for letrozole (96 hours). A likely consequence is the plasma steady-state drug level of 7 days achieved for anastrozole and exemestane and of 60 days for letrozole (Buzdar et al 2002).

All three third-generation AIs effectively reduce estradiol (E2), estrone (E1), and estrone-sulfate (E1S) plasma levels. One prospective trial compared the plasma E1, E1S, and E2 suppression after 6 weeks of treatment with either anastrozole or letrozole in postmenopausal patients with advanced disease. Letrozole was shown to be a slightly more potent suppressor of plasma oestrogen levels and total body aromatization compared to anastrozole (Geisler et al 2002). The clinical significance of this observation is so far unclear. There are to date no direct comparative studies involving exemestane. Additionally, some studies have suggested that AIs have the capability to reduce the production of intratumoral estrogens (Buzdar et al 2002).

Clinical development of aromatase inhibitors

Advanced breast cancer: rationale for use in adjuvant setting

The superiority of third-generation AIs over megestrol acetate in second-line therapy of advanced breast cancer led to the decision to challenge tamoxifen in first-line metastatic as well as adjuvant settings.

Two pivotal, large, randomized trials subsequently showed anastrozole to significantly improve time-to-progression (TTP) compared to tamoxifen in postmenopausal women with HR+ve advanced breast cancer (10.7 months vs 6.4 months, $p = 0.022$) (Bonnetterre et al 2000, 2001; Nabholz et al 2000). A further combined analysis at a median follow-up of 44 months also showed that anastrozole was at least as effective as tamoxifen in terms of overall survival (Nabholz et al 2003). Tolerability benefits were reported, with anastrozole having significantly fewer thromboembolic events and a lower incidence of vaginal bleeding compared to tamoxifen. No difference was observed between the two treatment in terms of hot flushes, bone fractures, or pain.

In the same setting, letrozole was reported to be superior to tamoxifen in a large, randomized, double-blind trial with significantly improved response rates and time-to-progression (9.4 months and 6 months, $p = 0.0001$) (Mouridsen et al 2003). The tolerability profile was also more favorable for

letrozole with a decreased incidence of thromboembolic events. No difference was noted between the therapies in terms of hot flushes, arthralgias, or bone pain. However, there was a suggestion that letrozole may slightly increase the cholesterol plasma levels.

In another randomized phase III trial, exemestane showed significant improvements compared to tamoxifen in terms of response rate (46% vs 31%, $p < 0.05$), clinical benefit (66% vs 49%, $p < 0.05$), and time-to-progression (10 months vs 6 months, $p < 0.05$) (Paridaens et al 2004). The safety profile was also favorable for exemestane with fewer hot flushes and a suggestion that the steroidal AI may have no impact on the bone and lipid metabolisms.

Only one randomized open-label phase IIIb/IV trial has compared two AIs (letrozole vs anastrozole) in advanced breast cancer previously treated with an anti-oestrogen (Rose et al 2003). The overall response rate (ORR) was significantly higher with letrozole (19.1% vs 12.3%, $p = 0.013$), but there was no difference between the treatment arms in terms of clinical benefit and TTP. Both agents were well tolerated and there were no significant differences in safety profiles.

Aromatase inhibitors as adjuvant treatment for breast cancer

Results from the EBCTCG trialists panel confirmed that, before the emergence of third-generation AIs, adjuvant tamoxifen for 5 years (only for hormonal receptor-positive disease) reduced the annual breast cancer death rate by 31%, irrespective of the use of chemotherapy, age, progesterone receptor status, or other tumor characteristics (EBCTCG 2005). Five years' duration of tamoxifen treatment was considered optimal, being significantly more effective than 10 years' or 2 years' and less. Moreover, two additional observations deserved to be mentioned:

1. The risk of recurrence is high in the first 5 years after a diagnosis of breast cancer, but with the highest peak within 2–3 years of diagnosis, independently of nodal status (Saphner et al 1996). This observation supports the upfront use of the most powerful new drugs (risk of early relapse)
2. For ER+ve tumors, the annual breast cancer mortality rates are similar during years 0–4 and 5–14, with 2/3 of deaths occurring between years 5 and 15. This observation is in favor of the potential increased duration of adjuvant endocrine therapies beyond 5 years, pending improved efficacy and good long-term toxicity profiles. Additionally, caution should be exercised when

interpreting overall survival data of adjuvant trials for endocrine sensitive breast cancers: longer median follow-ups, such as 8–15 years, are needed to fully evaluate the real impact of new endocrine treatments on overall survival.

Four different strategies were developed with third-generation AIs in adjuvant setting (see available results in Table 1):

1. The upfront strategy: As noted above, it appears highly important for women to receive the most effective adjuvant therapy at the first opportunity in order to minimize the early risk of relapse. Various trials compared AIs to tamoxifen for 5 years: anastrozole in the ATAC trial (ATAC Trialists' Group 2002, 2003, 2005), letrozole in the BIG 1–98 trial (Coates et al 2007), and exemestane in the TEAM trial (data not yet available). Anastrozole and letrozole were shown to be superior to tamoxifen in terms of disease-free survival, time to recurrence, time to distant recurrence, and incidence of contralateral breast cancer. Overall survival data are presently inconclusive, most likely because of short median follow-ups for survival (ATAC: 68 months and BIG 1-98: 51 months).
2. The sequential strategy: It could be important to introduce the most effective adjuvant therapy when the risk of tamoxifen resistance is the highest (after the 2nd year). The BIG 1-98 trial is the only study with a 4-arm design comparing the 5-year sequence of either tamoxifen followed by letrozole or the inverse (letrozole followed by tamoxifen) to either 5 years of tamoxifen or letrozole. To date, no prospective data are available comparing upfront AIs to a sequence of tamoxifen-AI. Results from the sequential part of the BIG 1-98 study with letrozole will be available in the future. These data are eagerly awaited as this is the only trial comparing 5 years of AI with 2 sequential strategies (tamoxifen-letrozole and letrozole-tamoxifen), which will resolve the conceptual debate 'sequential tamoxifen-AI versus upfront AI'.
3. Switch strategy: Switching to an AI after 2 or 3 years of tamoxifen for patients presently on tamoxifen (total of 5 years) has been evaluated with either exemestane: IES (Coombes et al 2004, 2007) or anastrozole: ITA trial (Boccardo et al 2005a, b) and ABCSG8/ARNO studies (Jakecz et al 2005a). The switch strategy has frequently been confounded with the sequential strategy. The difference between the two approaches lies in the fact that the switch trials censor patients who have relapsed during the first 2–3 years on tamoxifen, thus selecting a

subpopulation of patients with higher endocrine sensitivity (as we can assume that patients who relapse early might be the least sensitive to hormonotherapy). Sequence trials include all patients from the onset of adjuvant endocrine therapy and thus all patients relapsing on tamoxifen during the first 2–3 years of treatment are included as events in the trial analysis without any selection from the standpoint of endocrine sensitivity. As a consequence it is fallacious to use switch trials to reach conclusions on sequential strategies. Switching from tamoxifen to exemestane or anastrozole was reported to significantly improve disease-free survival and time to distant recurrence compared to continuing tamoxifen. Additionally, improved survival data are presently emerging with both AIs.

4. Extended hormonotherapy strategy: The duration of hormonal treatment in adjuvant situation is an old question, but remains a fundamental issue. Results from the EBCTG analysis (EBCTCG 2005) clearly demonstrated that 5 years of adjuvant tamoxifen therapy was better than shorter durations. However, data from the National Surgical Adjuvant Breast Project (NSABP) B-14 trial failed to demonstrate a positive impact of prolonged tamoxifen treatment (10 years vs 5 years). This was related not only to a worse toxicity profile seen with prolonged tamoxifen, but also to decreased efficacy, most likely related to the estrogen agonist effect seen with long-term use of tamoxifen (Fisher et al 2004).

Considering the facts that adjuvant tamoxifen induced a carry-over effect at 10 and 15 years even when the treatment was stopped early, and that there is a significant incidence of endocrine-sensitive patients having late relapses after 5–15 years (EBCTCG 2005), the third-generation AIs were considered good candidates for trying to optimize the duration of adjuvant therapy while potentially taking advantage of the sequential approach. This led to two trials, both evaluating the role of introducing an AI after 5 years of adjuvant tamoxifen: one with letrozole vs placebo, National Cancer Institute of Canada (NCIC) MA 17 (Goss et al 2003, 2005) and the other one with anastrozole ABCSG 6a (Jakecz et al 2005b; Schmid et al 2003). A third trial involving exemestane (NSABP B-33) was closed after publication of the results of the MA17 study (Table 1).

The AI prolonged trials with letrozole and anastrozole demonstrate the benefit of extending hormonal therapy beyond 5 years of tamoxifen. These results raise the question of the duration of adjuvant hormonal therapy beyond 5 years as well as the potential role played in these trials by the sequencing tamoxifen-AI.

Table 1 AIs results from adjuvant trials

Studies	ATAC (ATAC Trialists' group 2005)	BIG 1-98 (first part) (Coates 2007)	IES (Coombes 2007)	ITA (Boccardo 2005a)	ABCSG ARNO (Jakesz 2005a)	MA-17 (Goss 2005)	ABCSG 6a (Jakesz 2005b)
Schedule	Upfront TAM 5 years vs anastrozole 5 years	Upfront TAM 5 years vs letrozole 5 years	Switch: TAM vs exemestane after 2–3 years of TAM – total of 5 years	Switch: TAM vs anastrozole after 2–3 years of TAM – total of 5 years	Switch: TAM vs anastrozole after 2–3 years of TAM – total of 5 years	Extended HT: letrozole vs placebo after 5 years of TAM	Extended HT: anastrozole vs placebo after 5 years of TAM
Nb patients	6241	4922	4724	448	3224	5187	856
Median follow-up	68 months	51 months	55 months	36 months	28 months	30 months	60 months
Disease-free survival	A > T HR = 0.83 p = 0.005	L > T HR = 0.82 p = 0.004	E > T HR = 0.75 p = 0.0001	A > T HR = 0.42 p = 0.0001	A > T HR = 0.60 p = 0.0009	L > Placebo HR = 0.60 p = 0.002	A > Placebo HR = 0.64 p = 0.04
Time to recurrence	A > T HR 0.74 p = 0.0002	L > T HR 0.78 p = 0.004	N/A	N/A	N/A	N/A	N/A
Overall survival	NSD	NSD	E > T HR = 0.83 p = 0.05	NSD	A > T HR = 0.71 p = 0.038	NSD	NSD

Abbreviations: NSD, Not statistically different; N/A, not available; A, anastrozole; L, letrozole; E, exemestane.

The real questions beyond these all these results are: How long should we expose the patients to AIs in adjuvant setting? Should we go beyond 5 years? Should we start AI upfront and for how long? Beyond the decision making of using AIs and how to use them in adjuvant setting remains the choice of AI to use among the 3 agents available in the clinic. There is no direct comparison between the molecules in adjuvant setting and thus the decision to use either agent should be based upon their respective efficacy and most importantly their respective toxicity profiles with maturity of data and availability of results in the various reviewed clinical strategies.

Toxicity profile of aromatase inhibitors

It is critically important to prospectively assess the long term side-effect profile of AIs, as these agents have entered the adjuvant setting while the present recommendation for the duration of adjuvant endocrine therapy is 5 years. Because of short median exposure to hormone therapy, safety reports acquired from advanced breast cancer trials are usually sketchy, underestimating the toxicity profile of new endocrine agents. At best, they provide some guidance to prospectively design the assessment of adverse events in adjuvant studies. Getting long-term prospective toxicity

information is critical to evaluate the therapeutic index for new hormone therapy such as AIs.

Overall, the rate of adverse events (AE) did not differ with anastrozole compared to tamoxifen in the ATAC trial (68 months median follow-up: respectively 93.9% vs 94.6%, p = ns) while the rate of drug-related AE leading to withdrawal was lower for patients treated with anastrozole (6.5% vs 8.9%, p = 0.0005) (ATAC Trialists' Group 2005). In the BIG 1-98 trial with median follow-up of 51 months, more AE were observed with letrozole compared to tamoxifen (93.6% vs 88.4%) (Coates et al 2007). No difference in AE was reported in the IES between exemestane and tamoxifen (median follow-up: 55 months; respectively 92.5% vs 92.6, p = ns) (Coombes et al 2007).

In the ATAC trial, the incidence of serious adverse events (SAE) was significantly lower with anastrozole vs tamoxifen (33.3% vs 36%, p = 0.03) while drug-related SAEs were less frequently seen with anastrozole (4.7% vs 9.0%, p = 0.0001). Life-threatening SAE were reported in similar proportion between letrozole and tamoxifen in the BIG 1-98 study (respectively 4.6% vs 3.8%) as were Grade 3–4 AEs with exemestane versus tamoxifen in the IES (respectively 18.4% vs 17.6%).

When reviewing all side-effects induced by long-term use of AIs versus tamoxifen, a trend seems to emerge (Table 2).

Table 2 Summary of adverse events of aromatase inhibitors (AIs)

Class effect of AIs:	
• Favorable to AIs	<ul style="list-style-type: none"> ○ Hot flushes and night sweats ○ Gynecologic events ○ Thromboembolic disease
• Unfavorable to AIs	<ul style="list-style-type: none"> ○ Skeletal complications ○ Arthralgia and musculoskeletal pain ○ Sexual dysfunction
Non-class effects of AIs, specific to given AIs:	
○ Lipid metabolism	
○ Cardiac events	
○ Cerebrovascular events	
○ Other adverse events	<ul style="list-style-type: none"> ○ Gastrointestinal ○ Urogenital ○ Neurologic ○ Visual disturbances

A first series of side-effects appears to be specific and favorable to AIs (hot flushes, gynecologic side-effects and cardio-vascular events including thromboembolism), a second series specific to all AIs but favorable to tamoxifen (bone fractures/ osteoporosis and arthralgia), and a third series more specific to a given AI (lipid metabolism, cardiac, cerebrovascular, and others).

Class effects of AIs, favorable to AIs

Hot flushes and night sweats

Hot flushes are frequently observed in adjuvant studies with endocrine agents with a usually high incidence, independently of the type of hormone therapy used, including placebo. Consequently, hot flushes were prospectively assessed in the main adjuvant trials with AIs. In the ATAC study, the rate of hot flushes was significantly lower with anastrozole compared to tamoxifen (35.7% vs 40.9%, $p < 0.0001$). The BIG 1–98 study found also a significant improvement in favor of letrozole vs tamoxifen for hot flushes (respectively 32.8% vs 37.4%, $p < 0.001$) and night sweats (respectively 14.2% vs 17.0%, $p = 0.007$). However, when compared to placebo in the MA 17 trial, patients on letrozole experienced more hot flushes (58% vs 54%, $p = 0.003$). In contrast, a higher incidence of hot flushes and menopausal symptoms was reported with exemestane compared to tamoxifen in the IES, although without reaching the level of statistical significance (hot flushes: 42.4% vs 39.9%, $p = 0.08$; menopausal symptoms: 47.8% vs 45.1%, $p = 0.06$).

Gynecologic (Table 3)

Tamoxifen is known to have an oestrogenic effect on healthy endometrial tissue with consequences such as endometrial

proliferation and thickening. Long-term use of tamoxifen has previously been associated with an increased risk of polyp formation, vaginal bleeding, and increased incidence of endometrial cancer (Bissett et al 1994; EBCTCG 2005.). In contrast, AIs induce uterine atrophy and may decrease tamoxifen-induced changes, secondary to a prior course of therapy.

As expected when compared to tamoxifen, AI therapy resulted in fewer gynecological AEs. In the ATAC trial, gynecologic events (including endometrial hyperplasia, endometrial neoplasia, cervical neoplasia, and enlarged uterine fibroids) were less frequent with anastrozole compared to tamoxifen (3.0% vs 10.0%; $p < 0.0001$). As well, a lower incidence of gynecologic SAEs was reported with exemestane versus tamoxifen in the IES (5.9% vs 9.0%; $p = 0.0002$).

When prospectively assessed, vaginal bleeding was significantly less frequent with anastrozole than tamoxifen in the ATAC study (5.4% vs 10.2%; $p < 0.0001$), as with letrozole in the BIG 1–98 trial (3.8% vs 8.3%; $p < 0.0001$) and exemestane in the IES (4.6% vs 6.5%; $p < 0.008$). The ABCSG 8/ARNO 95 trials reported the combined incidence of vaginal bleeding and discharge, showing no difference between anastrozole and tamoxifen (18% vs 17%; $p = 0.93$). However, these safety results should be viewed with caution in these combined trials as adverse events were not prespecified in the ARNO 95 study protocol. Interestingly, when letrozole was compared to placebo in the MA17 trial, vaginal bleeding was more frequent in patients treated with the placebo, confirming the uterine effect of letrozole (8.0% vs 6.0%; $p = 0.005$). One consequence of vaginal bleeding is to mandate further investigations to rule out endometrial hyperplasia or cancer. In the ATAC study, significantly fewer patients on anastrozole underwent hysterectomies compared with those treated with tamoxifen (1.3% vs 5.1%; $p < 0.0001$). In the IES, the rate of uterine dilatation and curettage was significantly lower with exemestane compared to tamoxifen (0.6% vs 1.4%; $p = 0.009$) and significantly fewer patients treated with exemestane were diagnosed with endometrial hyperplasia (0.1% vs 1.0%; $p < 0.0001$) and uterine polyps/fibroids (1.2% vs 3.2%; $p < 0.0001$) compared to those on tamoxifen. Of note, in this trial, the rate of hysterectomy was similar between the two treatment groups.

Vaginal discharge is usually related to a postmenopausal deficit in estrogen, vaginal atrophy, and alkalinity. In the ATAC trial, fewer patients on anastrozole experienced vaginal discharge compared to those treated with tamoxifen (3.5% vs 13.2%; $p < 0.0001$). In addition vaginal moniliasis was more frequently diagnosed for patients on tamoxifen versus anastrozole (4% vs 1%; $p < 0.0001$) (ATAC Trialists' Group 2006). Similarly, more patients on tamoxifen presented with

Table 3 Gynecologic side effects in adjuvant randomized trials comparing aromatase inhibitors to tamoxifen or placebo in breast cancer

Study	ATAC Anastrozole vs tam (ATAC group 2005)	BIG 1-98 Letrozole vs tam (Coates 2007)	ABCSG8/ARNO95 Anastrozole vs tam (Jakesz 2005a)	IES Exemestane vs tam (Coombes 2007)	MA 17 Letrozole vs Placebo (Goss 2005)
Median follow-up	68 months	51 months	55 months	36 months	28 months
Median exposure to AI	5 years	51 months	3 years	2-3 years	2 years
Gynecologic AEs	3% vs 10% p < 0.0001	N/A	N/A	N/A	N/A
Gynecologic SAEs	N/A	N/A	N/A	5.9% vs 9.0% p = 0.0002	N/A
Vaginal bleeding	5.4% vs 10.2% p < 0.0001	3.8% vs 8.3% p < 0.0001	18% vs 17% p = 0.93 ^b	4.6% vs 6.5% p = 0.008 ^a	6.0% vs 8.0% p = 0.005
Hysterectomy	1% vs 5% p < 0.0001	N/A	N/A	No difference	N/A
Uterine dilatation/ Curettage	N/A	N/A	N/A	0.6% vs 1.4% p = 0.009	N/A
Endometrial hyperplasia	N/A	N/A	N/A	0.1% vs 1.0% p < 0.0001	N/A
Uterine polyps/ fibroids	N/A	N/A	N/A	1.2% vs 3.2% p < 0.0001	N/A
Vaginal discharge	3.5% vs 13.2% p < 0.0001	N/A	N/A	2.8% vs 3.9% p = 0.04	N/A
Endometrial cancer	5 vs 17 p = 0.02	4 vs 16 p < 0.05	N/A	0.2% vs 0.4% p = ns	4 vs 11 p = 0.12
Vaginal dryness ^a	18.5% vs 9.1%	N/A	N/A	23.5% vs 26.3%	22% vs 19% p = 0.016
Dyspareunia ^a	17.3% vs 8.1%	N/A	N/A	14.9% vs 15%	N/A
Loss of libido ^a	34% vs 26.1%	N/A	N/A	41.2% vs 45.4%	N/A

^aQuality of life questionnaires.^bVaginal bleeding and discharge.**Abbreviations:** N/A, Not available; AEs, adverse events; SAEs, serious adverse events.

vaginal discharge compared to women treated with exemestane in the IES (3.9% vs 2.8%; p < 0.04).

It has been established that the long-term use of tamoxifen bears an increased risk of endometrial cancer (EBCTCG 2005). Results with AIs confirm a decreased risk of endometrial cancer compared to tamoxifen. In the ATAC trial, 5 patients were diagnosed with endometrial cancers compared to 17 on tamoxifen (0.22% vs 0.76%; p = 0.02). Similar results were published with letrozole vs tamoxifen in the BIG 1-98 study (16 cases vs 4 cases; p < 0.05). For the switch trials, the incidence of endometrial cancer in the IES was doubled with tamoxifen compared to exemestane but did not reach the statistical significance (0.4% vs 0.2%, p = ns) while there was a trend for fewer endometrial cancers with anastrozole vs tamoxifen in the ABCSG8/ARNO95 combined studies (p = 0.069). Finally, when compared to placebo in the MA 17 trial, only 4 patients on letrozole were reported having an endometrial cancer compared to 11 on placebo (p = 0.12).

Thromboembolic disease (Table 4)

It is known that breast cancer patients may develop thromboembolic complications when physiological antithrombotic systems are defective or when prothrombotic activities overcome the normal physiological antithrombotic mechanisms (Schmitt et al 1999). Venous thromboembolism classically occurs in patients with clinically overt cancer and may develop at any stage of the disease (Agnelli 1997). Treatments such as chemotherapy and certain endocrine therapies have been shown to further compound the risk of thromboembolic complications. In breast cancer patients undergoing chemotherapy, the incidence of thrombosis has been reported to range from 1.3% (stages I-III) to 17.6% (stage IV), with the highest risk observed in postmenopausal patients (Levine 1997). Tamoxifen has also been associated with a small but significant increased risk of venous thromboembolism, which is further worsened by the addition of chemotherapy. This increase in thromboembolic disease seen with tamoxifen is considered to be a consequence of its partial oestrogen receptor-agonist activity in certain tissues (Schmitt et al 1999).

Table 4 Cardiovascular side effects in adjuvant randomized trials comparing aromatase inhibitors to tamoxifen or placebo in breast cancer

Study	ATAC Anastrozole vs tam (ATAC group 2005)	BIG 1–98 Letrozole vs tam (Coates 2007)	ABCSG8/ARNO95 Anastrozole vs tam (Jakesz 2005a)	IES Exemestane vs tam (Coombes 2007)	MA 17 Letrozole vs Placebo (Goss 2005)
Median follow-up	68 months	51 months	55 months	36 months	28 months
Median exposure to AI	5 years	51 months	3 years	2–3 years	2 years
All cardiac events	N/A	5.5% vs 5.0 8.3% P = 0.48	N/A	16.5% vs 15.0% p = 0.16a	5.8% vs 5.6% p = 0.76
• Cardiac events	N/A	74 pts vs 35 pts p = 0.05	N/A	N/A	N/A
Grade 3–5 Ischemic cardiovascular disease	4.1% vs 3.4% p = 0.10	2.2% vs 1.7% p = 0.21	N/A	8.0% vs 6.9% p = 0.08	N/A
• Angina	2.0% vs 1.5% p = 0.07	N/A	N/A	N/A	1.2% vs 0.9% p = ns
• Myocardial infarction	1.0% vs 1.0% p = 0.5	N/A	≤1.0% vs ≤1.0% p = 1.0	1.3% vs 0.8% p = 0.08	0.3% vs 0.4% p = ns
• Grade 3–5 CVA/TIA	N/A	42 pts vs 21 pts p = 0.05	N/A	N/A	N/A
	2.0% vs 3.0% p = 0.03	1.4% vs 1.4% p = 0.90	N/A	2.5% vs 2.4% p = 0.89	0.7% vs 0.6% p = ns
Thromboembolic disease	3.0% vs 5.0% p = 0.0004	2.0% vs 3.8% p = 0.001	Fewer on anastrozole p = 0.034	1.2% vs 2.3% p = 0.004	0.4% vs 0.2% p = ns

^aVaginal bleeding and discharge.

Abbreviations: N/A, not available; ns, not significant; CVA/TIA, cerebro-vascular accident/transient ischemic attack.

Third-generation AIs, however, are potent inhibitors of oestrogen synthesis and have all been shown to significantly reduce the risk of thromboembolism compared with tamoxifen treatment in postmenopausal women with breast cancer. Both upfront therapy trials (ATAC and BIG 1–98) reported significant decreases in the rate of thromboembolic complications with the AI compared to tamoxifen (anastrozole: 3% vs 5%, $p = 0.0004$; letrozole: 2.3% vs 3.8%, $p < 0.001$). As well, in switch trials (IES and ABCSG 8/ARNO 95), exemestane induced fewer thromboembolic events compared to tamoxifen (1.2% vs 2.3%, $p = 0.004$) and there were fewer thromboses on anastrozole vs tamoxifen ($p = 0.034$), with a trend for fewer embolic events on anastrozole ($p = 0.064$). Lastly, when comparing letrozole to placebo in the MA 17 study, there was no significant difference in terms of thromboembolic events between the two patient groups.

Class effects of AIs, favorable to tamoxifen

Skeletal complications (Table 5)

Tamoxifen is known to have a positive effect on bone mineral density in postmenopausal breast cancer patients (Powles

et al 1996), but to date, tamoxifen has not been evaluated in a prospective trial in women with osteoporosis.

Patients treated in all the adjuvant large-scale randomized trials with anastrozole, letrozole, or exemestane clearly had an increasing rate of skeletal disorders, particularly osteoporosis and bone fractures, even in trials in which they were compared to placebo.

In the ATAC trial, anastrozole was associated with a significant increased incidence of fractures compared to tamoxifen (11.0% vs 7.7%, $p < 0.0001$). While the incidences of hip fractures (fracture type associated with high morbidity and mortality) and wrist fractures were similar for anastrozole and tamoxifen (respectively, 1.2% vs 1.0%, $p = 0.5$ and 2.3% vs 2.0%, $p = 0.4$), the difference was significant in favor of tamoxifen for spinal fractures (1.5% vs 0.9%, $p = 0.03$) and all other sites of fractures (7.1% vs 4.6%, $p < 0.0001$). Interestingly, the yearly fracture rate on anastrozole increased sharply compared to tamoxifen during the first 2 years of therapy before stabilizing, with a relative risk of fracture remaining constant with longer duration of treatment (ATAC Trialists' Group 2006). Finally at completion of therapy, the fracture rate reversed back to the lower rate observed with

Table 5 Fractures and arthralgia in adjuvant randomized trials comparing aromatase inhibitors to tamoxifen or placebo in breast cancer

Study	ATAC Anastrozole vs tam (ATAC group 2005)	BIG 1-98 Letrozole vs tam (Coates 2007)	ABCSG8/ARNO95 Anastrozole vs tam (Jacekz 2005a)	IES Exemestane vs tam (Coombes 2007)	MA 17 Letrozole vs Placebo (Goss 2005)
Median follow-up	68 months	51 months	55 months	36 months	28 months
Median exposure to AI	5 years	51 months	3 years	2-3 years	2 years
Fractures	11.0% vs 7.7% ^a p < 0.0001	8.6% vs 5.8% ^a p < 0.001	2.0% vs 1.0% ^b p = 0.015	4.3% vs 3.1% ^b p = 0.03	5.3% vs 4.6% ^b p = 0.25
Arthralgia	35.6% vs 29.4% ^a p < 0.0001	8.3% vs 3.8% ^b p < 0.0001	N/A	18.6% vs 11.8% ^b p < 0.0001	25.0% vs 21.0% ^b p < 0.001

^aPrespecified.^bNot prespecified.**Abbreviation:** N/A, not available.

tamoxifen (Locker and Eastell 2003). As expected, in the ABCSG/ARNO trial, there were significantly more fractures in patients switching to anastrozole versus those continuing on tamoxifen (2.4% vs 1.2%, $p = 0.015$).

Letrozole also bears an increased risk of fractures on the head-to-head comparison with tamoxifen (8.6% vs 5.8%, $p < 0.001$) (Coates et al 2007). A more detailed analysis of osteoporosis and bone fractures was published for the MA17 trial exploring the impact of extending treatment with letrozole compared to placebo (Goss et al 2005). More patients receiving letrozole had a new diagnosis of self-reported osteoporosis (8.1% vs 6.0%, $p = 0.003$) with a median time to occurrence of 0.70 years for those receiving letrozole and 0.52 years for those receiving placebo. Of a total of 256 patients who experienced a clinical fracture during the study period, 137 (5.3%) were taking letrozole and 119 (4.6%) were on placebo ($p = 0.25$). The median time to fracture was 1.06 year letrozole and 0.86 year for the placebo.

Even if preclinical data suggested that exemestane may yield a protective effect on bone metabolism, IES reported an increased incidence of osteoporosis with exemestane compared to tamoxifen (7.3% vs 5.5%, $p = 0.01$). Similarly, bone fractures were more frequent in the exemestane group compared to the tamoxifen group (4.3% vs 3.1%, $p = 0.03$) (Coombes et al 2007).

Despite these results, there is today no skeletal contraindication to the use of AIs in adjuvant setting. However, it is strongly recommended for patients, in particular for those with risk factors of osteoporosis, to determine the bone mineral density (BMD) status and the phosphocalcic metabolism, before initiating an AI therapy (Winer et al 2005). In case of normal upfront BMD, it is advised to proceed with another test at completion of adjuvant treatment with AI. In case of upfront osteopenia, another BMD should be performed after 1-2 years on AI therapy. Finally, an upfront osteoporotic

result should lead to the possible use of bisphosphonates concomitantly with the AI following promising preliminary reports showing a positive impact of bisphosphonates on the prevention of osteoporosis (Gnant et al 2004).

Arthralgia and musculoskeletal pain (Table 5)

In clinical practice, the main symptomatic issue with AIs remains arthralgias and fibromyalgias for which no clear physiopathological explanation is known and no specific treatment defined. Their assessment in the various adjuvant trials with AIs has been complex, mostly because of a lack of clear definition (arthralgia, arthritis, osteoarthritis, myalgia, muscle cramps, fibromyalgia, bone pain, musculoskeletal pain).

In the ATAC trial, arthralgia was a predefined adverse event and was recorded as a grouping of arthralgia, arthritis, arthrosis, and joint disorders (Buzdar et al 2006). Significantly more patients treated with anastrozole presented with arthralgia compared to those on tamoxifen (35.6% vs 29.4%, $p < 0.0001$). The median time to first event was 13.9 months for anastrozole and 17.7 months for tamoxifen. Serious events were noted in similar proportions between the two treatment groups (10.6% for anastrozole and 10.4% for tamoxifen). Few patients from either group withdrew from treatment because of arthralgia (13 vs 6). More than 50% of patients with joint symptoms received treatment for pain management. More than 90% of these patients were managed with nonsteroidal anti-inflammatory drugs alone or in combination with other mild analgesics. As nonpre-specified adverse events, muscle cramps were more frequent with tamoxifen than anastrozole (8% vs 4%, $p < 0.0001$) while carpal tunnel syndrome was observed more with anastrozole (3% vs 1%, $p < 0.0001$). In the switch portion of the Austrian ABCSG 8 trial, bone pain was more frequent with anastrozole compared to tamoxifen ($p = 0.054$).

Arthralgia and myalgia were not prespecified in the BIG 1–98 trial, but were part of an ‘other’ category and thus could be underestimated. Nevertheless, letrozole induced more arthralgia than tamoxifen (20.0% vs 13.5%, $p < 0.001$). When looking at the grading according to the National Cancer Institute Common Toxicity Criteria (version 2.0), the great majority of patients with arthralgia in the letrozole arm suffered grade 1–2 (444 pts of 489, 90.8%) with only 43 cases of grade 3 (8.8%) and 2 cases of grade 4 (0.4%). There was no significant difference in terms of myalgia between the 2 treatment groups ($p = 0.19$). Interestingly, the MA 17 trial comparing letrozole to placebo found more patients with myalgias in the letrozole arm (15% vs 12%, $p = 0.004$) while bone pain was recorded in comparable proportion of cases between the 2 arms (letrozole: 5% vs placebo: 6%, $p = 0.67$). Nevertheless, arthralgias were more frequent with letrozole compared to placebo (25% vs 21%, $p < 0.001$).

In the switch IES, there was a higher frequency of arthralgia in the exemestane group compared to tamoxifen (18.6% vs 11.8%, $p < 0.0001$). The incidence of arthritis was also higher with exemestane (14.1% vs 12.0%, $p < 0.03$) while osteoarthritis was reported in similar proportion between the two treatment groups (8.7% vs 7.4%, $p = 0.113$). Carpal tunnel syndrome was more frequent on exemestane versus tamoxifen (2.8% vs 0.0%, $p < 0.0001$). Finally, musculoskeletal pain was observed in 21% of patients on exemestane versus 16% for those on tamoxifen ($p < 0.0001$).

Sexual dysfunction (Table 3)

Sexual dysfunction is a frequent event for patients treated with endocrine therapy, although potentially under-reported in breast cancer studies. Sexual dysfunction was usually assessed in the various adjuvant trials with AIs either as non predefined adverse events (vaginal dryness, dyspareunia, loss of libido) or as part of quality of life (QoL) modules (Whelan et al 2005; Cella et al 2006; Fallowfield et al 2006). Secondary to low estrogen levels, vaginal dryness can induce dyspareunia as well as decreased libido. As expected, vaginal dryness was more frequently seen with AIs compared to tamoxifen in the ATAC and MA 17 trials. More patients on anastrozole than tamoxifen reported dyspareunia (28 vs 9, $p = 0.002$) and decreased libido (39 vs 12, $p = 0.0001$) (Cella et al 2006). Quality of life studies in the MA 17 trial showed a significant worsening of the parameters of the sexual domain with letrozole compared to placebo (Whelan et al 2005). As well, sexual dysfunction was also observed with exemestane

in the IES, but without reaching the statistical significance when compared to tamoxifen (Fallowfield et al 2006).

Side effects specific to given AIs

Lipid metabolism

Postmenopausal women are known to have increased levels of low-density lipoprotein cholesterol (LDL-C) and decreased levels of high-density lipoprotein cholesterol (HDL-C) compared to premenopausal women of the same age, and these unfavorable changes are considered to be a risk factor for the development of coronary heart disease (Gorodeski 2002). There is no clear evidence that tamoxifen favorably influences the lipid metabolism especially when considering the results from the Women’s Health Initiative study (Rossouw et al 2002). It is, therefore, important to ascertain whether or not long-term treatment with anastrozole, letrozole, or exemestane has an impact on the lipid parameters.

Anastrozole was first assessed in advanced breast cancer studies in a combined analysis of the North American and Tamoxifen or Arimidex Randomized Group Efficacy and Tolerability (TARGET) trials. This study on 600 postmenopausal patients concluded that neither anastrozole nor tamoxifen had a clinically significant impact on total cholesterol (Dewar et al 2000). Other studies in metastatic breast cancer, consistent with this analysis, showed no significant change in total cholesterol, LDL-C, HDL-C, or triglycerides. Furthermore, there was no change in the atherogenic risk ratios of total cholesterol/HDL-C and LDL-C/HDL-C (Wojtacki et al 2004).

In early breast cancer, a small study evaluated the effects of anastrozole on lipid profiles of 54 postmenopausal women. Anastrozole induced no significant change of serum levels of apolipoprotein A1, apolipoprotein B, triglycerides, total cholesterol, HDL-C, and LDL-C. Atherogenic risk ratios (total cholesterol/HDL-C, LDL-C/HDL-C and apolipoprotein A1/apolipoprotein B) were stable from baseline to various measurements at 1, 3, 6, and 12 months (Wojtacki et al 2005). Additionally, potential changes in serum lipid profiles were investigated in a neoadjuvant randomized trial ($n = 176$) comparing anastrozole or tamoxifen alone or in combination. Treatment with either tamoxifen or anastrozole for 12 weeks was associated with a significant increase of HDL-C levels in both groups, whereas total cholesterol decreased in the tamoxifen group and increased in the anastrozole group, although not significantly (Banerjee et al 2005). Following these results with anastrozole on lipid parameters in advanced breast cancer, serum lipid levels were not prospectively studied in the ATAC trial. Hypercholesterolemia was assessed

as a nonpre-defined adverse event and results showed an increased incidence with anastrozole versus tamoxifen in the 'completion of 5 years' treatment analysis' (9% vs 3%, $p < 0.0001$) (ATAC Trialists' Group 2006).

The impact of letrozole on lipid composition was initially measured in a small study of 20 postmenopausal women with advanced breast cancer. Results showed a significant increase in total cholesterol ($p = 0.05$), LDL-C ($p < 0.01$) and apolipoprotein B levels ($p = 0.05$) after 16 weeks of treatment. In addition, there was evidence of unfavorable changes in the atherogenic risk ratios of total cholesterol/HDL-C ($p < 0.005$), LDL-C/HDL-C ($p < 0.005$) and apolipoprotein A1/apolipoprotein B ($p = 0.005$) (Elisaf et al 2001). Consequently, hypercholesterolemia was prospectively studied in the BIG 1-98 trial. Results showed a significantly higher prevalence for hypercholesterolemia in patients treated with letrozole versus those receiving tamoxifen (respectively 50.6% vs 24.6%, $p < 0.001$). However, the great majority (99%) of these cases of hypercholesterolemia were graded 1 or 2 (Coates 2007). In contrast, the MA.17 lipid substudy showed no significant changes induced by letrozole on cholesterol (including LDL or HDL fractions) (16% vs 16%, $p = 0.79$), triglycerides or lipoprotein over a period of treatment of 3 years following 5 years of tamoxifen (Wasan 2005).

Exemestane was first evaluated in a 9-week study, in which plasma changes in advanced breast cancer patients demonstrated a significant decrease in total cholesterol ($p < 0.01$), triglycerides ($p = 0.023$) and apolipoprotein A1 ($p < 0.01$). Additionally, there was also a significant decrease in HDL-C ($p < 0.01$) and in the apolipoprotein A1/apolipoprotein B atherogenic risk ratio ($p < 0.01$) (Engan et al 1995).

In contrast, a substudy of an advanced breast cancer phase II randomized trial did not find the treatment with either exemestane or tamoxifen to have a significant effect on total cholesterol, HDL-C, apolipoprotein A1, or apolipoprotein B. However, at week 24, exemestane was associated with a significant increase in triglycerides ($p = 0.002$) (Atalay et al 2004). In the IES, there was no difference in hypercholesterolemia levels between patients on exemestane versus those treated with continued tamoxifen (7.2% vs 6.0%, $p = 0.12$) (Coombes et al 2007).

In terms of comparative studies between the AIs, an early breast cancer study compared the effects of adjuvant exemestane and anastrozole on serum lipids in postmenopausal women (Kataja et al 2002). After 12 weeks of treatment, exemestane and anastrozole had no clinically significant impact on total cholesterol, HDL-C, LDL-C or triglycerides compared with baseline. Anastrozole did, however, show

an increase in HDL-C levels whereas exemestane showed a decreased HDL-C levels. A second small randomized study, the Letrozole, Exemestane, and Anastrozole Pharmacodynamics trial (LEAP) compared the lipid profiles of 90 evaluable healthy volunteers, receiving either anastrozole (1 mg/day), letrozole (2.5 mg/day) or exemestane (25 mg/day) once daily for 24 weeks (McCloskey 2005). Results showed no significant changes of lipid parameters for women exposed to anastrozole. While letrozole induced a significant increase in triglycerides levels without effect on the atherogenic ratios. Exposure to exemestane resulted in a significant increase of the atherogenic ratios LDL-C/HDL-C and apolipoprotein B/apolipoprotein A1, compared to anastrozole and letrozole.

The molecular differences between anastrozole, letrozole, and exemestane, therefore, could not only affect the selectivity for the aromatase complex with small differences in plasma oestrogen suppression, but could also play a role in the small variations in lipid alterations induced by the third-generation AIs. Although these differences between the AIs may not significantly influence the clinical efficacy, it is unknown so far whether or not these modified lipid profiles may translate into a long-term increased risk of cardiovascular (CV) disease.

Cardiac adverse events (Table 4)

No cardiac safety issues were identified for any of the AIs in the advanced breast cancer setting. However, the duration of exposure to the drugs was relatively short and CV events were not a particular focus of safety analyses in these metastatic trials (Nabholtz and Glogorov 2006).

In the last analysis of the ATAC trial (68 months median follow-up), the incidence of ischemic cardiac disease was comparable for patients treated with anastrozole compared with those on tamoxifen (4.1% vs 3.4%, $p = 0.10$) (ATAC Trialists' Group 2005). There was a numerical increase, although not statistically significant, in terms of angina with anastrozole compared to tamoxifen (71 cases vs 51 cases, $p = 0.07$). However, this was not considered to be a safety concern, as there was no correlation with prolonged treatment, and the majority of events were mild to moderate in severity. Additionally, there was no difference in myocardial infarctions between anastrozole and tamoxifen at 68 months (37 cases vs 34 cases, $p = 0.7$) (ATAC Trialists' Group 2006) while the number of CV deaths was similar in the two treatment groups (49 vs 46, respectively).

In keeping with these data, no difference in myocardial infarctions were observed in the ABCSG 8/ARNO 95 trials for patients switching to anastrozole compared with those

continuing tamoxifen (2 cases vs 3 cases). Available CV data from the ITA trial are limited to the incidence of CV disease, which showed no significant difference between the tamoxifen group and the anastrozole group (9.3% and 7.9%, respectively; $p = 0.4$) (Boccardo et al 2005b).

The recent updated analysis of the BIG 1–98 trial, at 51 months median follow-up, reported no significant difference in incidence of any grade cardiac events between letrozole and tamoxifen (5.5% vs 5.0%, $p = 0.48$) (Coates 2007). However, patients on letrozole experienced a significantly greater incidence of grade 3–5 cardiac events than those on tamoxifen (74 cases vs 35 cases, $p < 0.05$). These events consisted mostly of ischemic heart disease (42 cases vs 21 cases, $p < 0.05$) and cardiac failures (24 cases vs 14 cases). Cardiac deaths were reported in 11 cases on letrozole and 5 on tamoxifen. Of particular interest is the fact that there was no clear evidence of correlation between cardiac deaths and the statistically significant increased number of hypercholesterolemia in the letrozole arm. Clearly, these results should be put in the context of the total number of deaths without cancer event (letrozole: 60 vs tamoxifen: 48) and the total number of deaths in the trial (letrozole: 194 vs tamoxifen: 211, $p = ns$) (Coates et al 2007).

Cardiovascular data from the MA17 (letrozole arm: 2593 patients and placebo arm: 2394 patients) showed no overall significant difference between letrozole and placebo in terms of CV disease (respectively 5.8% and 5.6%, $p = 0.76$), including myocardial infarction and new or worsening angina.

In the IES at 55 months' median follow-up, there was no significant difference in the overall incidence of CV events (excluding thromboembolism) between the two treatment arms (exemestane: 16.5% vs tamoxifen: 15.0%, $p = 0.16$) (Coombes et al 2007). The incidence of ischemic cardiovascular disease was comparable between the 2 arms (exemestane: 8.0% vs tamoxifen: 6.9%, $p = 0.17$) and, in contrast with preliminary reports, there was no statistically significant difference in terms of myocardial infarctions between patients on exemestane and those on tamoxifen (respectively 31 cases vs 19 cases, $p = 0.08$). Of particular note is the fact that 22 patients on exemestane (71%) had a prior history of high blood pressure compared to only 6 patients on tamoxifen. The number of deaths due to cardiac causes was very low in both arms.

Cerebrovascular adverse events (Table 4)

Consistent with the initial analyses of the ATAC study, ischemic cerebrovascular adverse events at 68 months were significantly reduced for patients treated with anastrozole

compared with those treated with tamoxifen (62 cases/2% vs 88 cases/3%, $p = 0.03$). This translated in 14 cerebrovascular deaths on anastrozole vs 22 on tamoxifen ($p = ns$).

None of the other adjuvant trials, with letrozole and exemestane, showed any evidence of decreased cerebrovascular events compared to tamoxifen or placebo. In the BIG 1–98 trial, there was no difference in the incidence of cerebrovascular adverse events/transient ischemic attack between letrozole and tamoxifen (1.4% vs 1.4%, $p = 0.90$). A total of 7 cerebrovascular deaths were reported, 4 on letrozole and 3 on tamoxifen. As well, the MA 17 showed a similar rate of cerebrovascular adverse events between letrozole and placebo (0.7% vs 0.6%, $p = ns$). Lastly, these events occurred in similar proportion between exemestane and tamoxifen in the IES (2.5% vs 2.4%, $p = 0.89$).

Other adverse events (Table 2)

The gastrointestinal toxicity of AIs is usually mild with no evidence of increased nausea/vomiting compared to tamoxifen or placebo. However, diarrhea appeared to be significantly more frequent with exemestane compared to tamoxifen in the IES (4.2% vs 2.2%, $p < 0.0001$) and with anastrozole in the ATAC trial (9% vs 7%, $p = 0.02$). However, no difference in diarrhea was noted between anastrozole and tamoxifen in the ABCSG 8/ARNO 95 study and between letrozole and placebo in the MA 17 trial.

Urogenital side-effects were only reported in the ATAC trial with a significant decreased incidence of urinary incontinence with anastrozole compared to tamoxifen (2.0% vs 4.0%, $p < 0.0001$) and less urinary tract infections for patients on the AI versus tamoxifen (8% vs 10%, $p = 0.002$).

Mild neurologic toxicity was recorded with anastrozole in the ATAC study consisting of paresthesia seen more frequently than with tamoxifen (7% vs 5%, $p = 0.0001$). Exemestane, as well, induced an increased incidence of paresthesia compared to tamoxifen in the IES (2.8% vs 1.0%, $p < 0.0001$).

High blood pressure was more frequent with anastrozole vs tamoxifen in the ATAC trial (13% vs 11%, $p = 0.04$) and with exemestane in the IES (35.8% vs 33.0%, $p = 0.05$). The MA 17 showed no difference between letrozole and placebo.

In terms of visual disturbances, there was no difference in the ATAC trial for cataracts (prespecified AE) between anastrozole and tamoxifen. Visual disturbances (unspecified types) were reported to be more frequent with exemestane vs tamoxifen in the preliminary analysis of IES at 30.7 months median follow-up (7.4% vs 5.7%, $p < 0.05$)

(Coombes et al 2004). However, there was no update on visual toxicity in the recent publication at median follow-up of 55 months (Coombes et al 2007).

Quality of life with of aromatase inhibitors

When considering the role of new endocrine therapy in early breast cancer, efficacy and safety with in particular the impact on quality of life (QoL) are today critical for decision making in the clinic.

In the ATAC trial, using the validated instrument Functional Assessment of Cancer Therapy – Breast plus Endocrine Subscale (FACT-B + ES) and despite different toxicity profiles recorded at 5 years median follow-up, no difference between anastrozole and tamoxifen were observed in terms of Trial Outcome Index (TOI) and its physical and functional components (Cella et al 2006). However, after an initial worsening of the TOI at 3 months follow-up, both treatments showed, compared to baseline, improvements in QoL over the rest of the 5-year period.

The impact on QoL of letrozole compared with placebo after 5 years of adjuvant tamoxifen was evaluated in the MA.17 trial, using the validated Short Form 36-item Health Survey (SF-36) and Menopause Specific Quality of Life (MENQOL) questionnaires (Whelan et al 2005). Published quality-of-life analysis for this study found no global differences between treatment groups in mean change scores from baseline for the SF-36 physical and mental component summary scores. On the response analysis, a significant difference in favor of placebo was seen between groups for the bodily pain domain ($p = 0.009$) and the vasomotor domain ($p = 0.001$) (Whelan et al 2005).

Exemestane was assessed, compared to tamoxifen, in the IES with the FACT-B instrument (Fallowfield et al 2006). There was no significant difference between the two treatment drugs in terms of TOI and its physical and functional components over a period of 2 years. Additionally, the mean endocrine subscale scores increased compared to baseline for both exemestane and tamoxifen.

Clinical issues from long-term toxicity profiles of AIs

Third-generation AIs have produced significant improvements in the treatment of early breast cancer for postmenopausal women. These agents have shown superiority over tamoxifen in both the initial adjuvant and switch settings and have induced improved outcome compared to placebo in the extended hormone therapy setting beyond 5 years of

tamoxifen. Despite no head-to-head trials comparing AIs in adjuvant setting, efficacy data for these agents may be relatively comparable in the different settings in which they were studied. However, in terms of safety profiles, results of adjuvant studies suggest that there may be some differences between these agents, confirming that today AIs should not be considered interchangeable in clinical practice (Winer et al 2005).

The full definition of long-term safety profiles for AIs is related to the maturity of available safety data. The situation is presently improving with reports on anastrozole at 68 months median follow-up and recent publications on letrozole and exemestane with, respectively, median follow-ups of 51 and 55 months. However, full safety data are required for all three agents over the full 5-year adjuvant treatment period before being able to fully determine their respective risk:benefit ratios.

With this goal in mind, 2 global risk-benefit indices were calculated for anastrozole in the ATAC trial, using the ‘completion of treatment’ analysis data (ATAC Trialists’ Group 2006). The first index is the validated Global Index of the Women’s Health Initiative (GI-WHI) based upon time to randomization to the earliest occurrence of breast cancer events, death, coronary heart disease, stroke, pulmonary embolism, endometrial cancer, colorectal cancer, and hip fracture. Results showed that patients treated with anastrozole had a lower incidence of events compared to those on tamoxifen (24% vs 27%, HR0.85, 95% CI: 0.77–0.94, $p = 0.0014$). The second indice is the Global Index of Disease-Free Survival and Serious Adverse Events (GI-DFS-SAE) constructed on the following events: time to recurrence, death, or any serious adverse events observed in the ‘completion of treatment’ 68 months median follow-up analysis of the ATAC study. The Global Index showed 1453 events (46%) for anastrozole and 1594 (51%) for tamoxifen (HR0.88, 95% CI: 0.82–0.94, $p = 0.0004$). Cumulative occurrence of events over time confirmed, for both indexes, a significant difference in favor of anastrozole appearing early, highest during the first 2 years of therapy and carried over the full 5 years of treatment (ATAC Trialists’ Group 2006).

Updated data are needed from the BIG 1-98 with a full 5 years exposure to letrozole in order to fully evaluate its risk-benefit ratio compared to tamoxifen in the adjuvant upfront endocrine therapy. While the duration of patient exposure to exemestane was limited to 2–3 years in the IES, it is difficult to draw firm conclusions on the long term toxicity profile of exemestane. In this regard, mature results from the

presently closed adjuvant TEAM study, comparing 5 years of exemestane to 5 years of tamoxifen as upfront adjuvant endocrine therapy for postmenopausal women, are eagerly awaited.

Conclusions

Third-generation AIs are now part of the armamentarium of endocrine therapy for postmenopausal patients with hormone-sensitive breast cancer. AIs results are consistently superior of those of tamoxifen. However, the best therapeutic strategies for AIs in adjuvant setting remain to be confirmed, in particular in terms of the role of the sequential approach and the duration of therapy beyond 5 years. While all three AIs have class adverse events either favorable (decreased incidence of hot flushes, gynecologic and thromboembolic side effects) or unfavorable (skeletal complications, arthralgia, musculoskeletal pain, sexual dysfunction), some variability between AIs has been reported in side effects such as lipid changes and cardiac events as well as gastrointestinal, urogenital, neurologic, and visual disturbances. All these safety data confirm that today AIs should not be considered interchangeable in clinical practice. First results of overall therapeutic index of AIs suggest superiority over tamoxifen with proven improved efficacy and better toxicity profile. Since there is no direct comparison between the three available AIs in adjuvant setting, the decision to use one specific AI should be based upon their respective efficacy and toxicity profiles, maturity of data and availability of results within the chosen clinical strategies.

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