An Overview of the Pharmacology and Pharmacokinetics of the Newer Generation Aromatase Inhibitors Anastrozole, Letrozole, and Exemestane

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BACKGROUND. The newer generation, nonsteroidal aromatase inhibitors (AIs) anastrozole and letrozole have shown superior efficacy compared with tamoxifen as first-line treatments and compared with megestrol acetate as second-line therapy in postmenopausal women with advanced breast carcinoma. In an open-label, Phase II trial, it was reported that exemestane showed numerical superiority compared with tamoxifen for objective response and clinical benefit. Because these agents ultimately may be administered for periods of up to 5 years in the adjuvant setting, it is of increasing importance to assess their tolerability and pharmacologic profiles.

METHODS. In the absence of data from direct clinical comparisons, the published literature was reviewed for the clinical pharmacology, pharmacokinetic characteristics, and selectivity profiles of anastrozole, letrozole, and exemestane.

RESULTS. At clinically administered doses, the plasma half-lives of anastrozole (1 mg once daily), letrozole (2.5 mg once daily), and exemestane (25 mg once daily) were 41–48 hours, 2–4 days, and 27 hours, respectively. The time to steady-state plasma levels was 7 days for both anastrozole and exemestane and 60 days for letrozole. Androgenic side effects have been reported only with exemestane. Anastrozole treatment had no impact on plasma lipid levels, whereas both letrozole and exemestane had an unfavorable effect on plasma lipid levels. In indirect comparisons, anastrozole showed the highest degree of selectivity compared with letrozole and exemestane in terms of a lack of effect on adrenosteroidogenesis.

CONCLUSIONS. All three AIs demonstrated clinical efficacy over preexisting treatments. However, there were differences in terms of pharmacokinetics and effects on lipid levels and adrenosteroidogenesis. The long-term clinical significance of these differences remains to be elucidated. ***Cancer* 2002;95:2006–16.**

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Breast carcinoma has become a major health problem over the past 50 years, affecting as many as one in eight women. It is the most common form of malignancy among women in North America, most of Europe, Latin America, and Australasia.[1,2] Although there have been substantial developments in its treatment, approximately 25% of women with breast carcinoma eventually will die from their disease.[3]

It has long been recognized that approximately one-third of all breast carcinomas are estrogen dependent and will regress after estrogen deprivation.[4] Thus, reducing the level of estrogen remains a valuable target for breast carcinoma treatment in both premeno-

pausal and postmenopausal women. Reducing the effects of estrogen can be mediated by agents that block estrogen at the receptor level, such as tamoxifen, or by inhibitors of estrogen biosynthesis, such as the aromatase inhibitors (AIs). AIs act through inhibition of the cytochrome P450 enzyme, aromatase, which catalyses the conversion of androgens to estrogens. The AIs have been developed primarily for use in women in whom ovarian function has ceased either in naturally or surgically postmenopausal patients.[5] It should be noted that, in premenopausal women, the ovaries are the primary site of estrogen production, and, because AIs are not capable of blocking ovarian estrogen synthesis completely in premenopausal women, they cannot be used as the sole endocrine treatment. In this patient group, there are data showing that anastrozole can be used in combination with ovarian ablation therapy with such drugs as goserelin (Zoladex™; a gonadotrophin-releasing hormone agonist) to ensure blockade of estrogen synthesis. Preliminary pharmacokinetic data for this combination are promising and show that 15 premenopausal patients with metastatic breast carcinoma who received anastrozole (1 mg once daily) with goserelin (3.6 mg monthly) for up to 41 months had significantly lower estradiol (E_2) levels ($P < 0.05$; measured at 6 months) compared with baseline levels.[6] In addition, 11 of those patients (73%) achieved either an objective response (OR) or stable disease after 6 months of treatment.[6]

The first-generation AI, aminoglutethimide, became available in the late 1970s.[7] However, despite its proven efficacy as second-line therapy after tamoxifen in postmenopausal women with advanced hormone-responsive breast carcinoma, its widespread use was limited by both toxicity and lack of selectivity for the aromatase enzyme, necessitating concomitant corticosteroid supplementation.[7] Formestane, which is a steroidal AI based on the androgen androstenedione that also has been shown as an effective treatment for this patient population and is a more selective AI, became available in 1993. Because of its improved selectivity, formestane has fewer side effects compared with aminoglutethimide; however, as a result of extensive first-pass metabolism, it has to be administered by twice-monthly intramuscular injection, and local reactions have been reported in up to 17% of patients.[8] More recently, the so-called *newer generation AIs*, which include anastrozole, letrozole, fadrozole (Japan only), and exemestane, have become available for use in postmenopausal women with advanced, hormone-responsive breast carcinoma.

Exemestane and formestane are classified as Type I AIs on the basis of their steroidal nature and irreversible binding to the aromatase enzyme, causing permanent inactivation even after the drug is cleared from the circulation. By contrast, anastrozole and letrozole, which are nonsteroidal, are classified as Type II AIs, because they competitively inhibit the conversion of androgens to estrogens. This class of drug also includes fadrozole, which is available only in Japan and is not discussed further in this review.

For second-line agents in the treatment of postmenopausal women with advanced breast carcinoma, it has been shown that anastrozole and exemestane offer significant benefits with respect to survival compared with the progestin *megestrol acetate* (MA).[9–11] Anastrozole increased the median survival (27 months vs. 23 months) ($P < 0.025$) and the proportion of patients surviving for 2 years (56% vs. 46%) compared with MA at 31 months of follow-up.[11] Likewise, treatment with exemestane produced increased time to disease progression (TTP; 4.6 months vs. 3.9 months) and was associated with a significant survival advantage compared with MA (median survival not reached vs. 28 months), although that study had a shorter median follow-up of 11.4 months.[10]

There are conflicting results with respect to the second-line use of letrozole (0.5 mg and 2.5 mg doses). In one Phase III study that investigated the effects of letrozole (0.5 mg and 2.5 mg doses), it was shown that patients who received the clinical dose of letrozole (2.5 mg) had a superior OR rate (24% vs. 16%), response duration, time to treatment failure (5.1 months vs. 3.9 months), and tolerability compared with patients who received MA.[12] However, more recently, the results of another Phase III study failed to replicate the earlier findings, with patients who received the higher dose of letrozole showing an OR rate equivalent to that of patients who received MA.[13] Both studies also reported no significant differences between the letrozole (2.5 mg) and MA groups with respect to the TTP and overall survival.[12,13] However, the study reported by Buzdar and colleagues[13] showed that the 0.5 mg dose of letrozole was significantly superior to MA with respect to TTP ($P = 0.044$) and time to treatment failure (TTF) ($P = 0.018$).[13]

In another Phase III randomized trial, letrozole (0.5 mg and 2.5 mg) proved superior to the prototype AI, aminoglutethimide, with respect to TTP ($P = 0.008$), TTF ($P = 0.003$), and overall survival (28 months vs. 20 months; $P = 0.002$).[14] There was a trend toward an improved response rate with the use of letrozole (20% vs. 12%), although this did not reach statistical significance ($P = 0.06$).

The place of tamoxifen as the gold standard for the first-line treatment of postmenopausal women with advanced breast carcinoma has been challenged recently by the newer generation AIs. In one Phase III

study in which 88.4% of patients (n = 312 of 353 patients) had estrogen receptor and/or progesterone receptor positive tumors, there was a significant increase in TTP in the anastrozole arm compared with the tamoxifen arm (anastrozole vs. tamoxifen: 11.1 months vs. 5.6 months for anastrozole vs. tamoxifen; hazard ratio [HR], 1.44; lower one-sided 95% confidence limit [95%CL], 1.16; $P = 0.005$).[15] Indeed, anastrozole was the first endocrine agent to show significant benefit over tamoxifen with respect to TTP in patients with hormone-sensitive tumors (HR, 1.13; lower one-sided 95%CL, 1.00; $P = 0.022$ and $P < 0.005$;[16] HR, 0.77; 95% confidence interval [95%CI], 0.56–0.91; $P = 0.047$[17]).

Data from a Phase III randomized study with letrozole also showed an improvement in terms of TTP in the overall population (66% of patients had estrogen receptor positive and/or progesterone receptor positive tumors) compared with tamoxifen (HR, 0.70; 95%CI, 0.60–0.82; $P = 0.0001$).[18] The TTP was significantly longer in the letrozole arm compared with the tamoxifen arm irrespective of hormone receptor status (HR, 0.70; 95%CL, 0.58–0.84; $P = 0.0002$), dominant site of disease (soft tissue: HR, 0.73; 95%CL, 0.53–1.00; $P = 0.05$; bone and/or soft tissue: HR, 0.70; 95%CL, 0.53–0.93; $P = 0.01$; visceral and/or other sites: HR, 0.69; 95%CL, 0.55–0.87; $P = 0.001$), and prior adjuvant antiestrogen therapy (prior therapy: HR, 0.68; 95%CL, 0.48–0.98; $P = 0.04$; no prior therapy: HR, 0.71; 95%CL, 0.60–0.84; $P = 0.0001$).[18] Furthermore, as primary systemic therapy, it has been reported that letrozole (2.5 mg once daily) produced a significantly superior OR rate compared with tamoxifen (20 mg once daily) ($P < 0.001$).[19]

Compared with anastrozole and letrozole, there are no published Phase III data that compare exemestane with tamoxifen as first-line therapy for patients with advanced breast carcinoma. The most recent update of a small, open-label, Phase II study of exemestane compared with tamoxifen showed a benefit in terms of OR for patients who received exemestane (45% vs. 14%), although there are no statistics available to date.[20]

Although, as a class, the newer generation AIs all show efficacy and tolerability benefits over previously established treatments, to date, there have been no direct comparisons between anastrozole, letrozole, and exemestane in terms of clinical outcome and tolerability. The individual pharmacologic, pharmacokinetic, and tolerability profiles of these drugs will take on increasing importance as they move rapidly toward use in the adjuvant setting, in which it is probable that they will be administered for periods of up to 5 years. It is the objective of the remainder of this review to consider these properties to help clinicians in the management of their patients who are receiving hormone therapy. Below, we review and discuss the data obtained from an extensive literature search of the Medline and EmBase data bases and from published abstracts at conferences from 1991 to January 2001.

Properties of the Ideal Drug

Reviewing the clinical pharmacology and selectivity of the newer generation AIs may provide an indication of which of the three agents most closely matches an *ideal* profile. The following considerations are important for any pharmacologic therapy to ensure optimal efficacy with as few adverse events as possible: 1) It should be effective at doses that exert maximal effect with minimum dose, avoiding unnecessary overexposure of patients to the drug. 2) It should achieve the intended clinical effect as swiftly as possible and should have a rapid onset of action. 3) The pharmacokinetic/pharmacodynamic half-life should be consistent with the intended/preferred dosing interval (e.g., once daily). 4) It should be cleared rapidly from the body upon cessation of treatment, so that the potential for adverse events is minimized. 5) There should be minimal drug-drug interactions. 6) It should be well tolerated and free from effects on other pharmacologic or physiologic processes. 7) It should be as selective as possible, only exerting its effect on the intended target.

Comparative Structure

Both anastrozole and letrozole are nonsteroidal AIs, whereas exemestane has a steroidal structure (Fig. 1). Exemestane has androgenic properties, and its use has been associated with steroidal-like side effects, such as weight gain and acne.[21–23] The extent of these steroidal side effects are discussed further below.

Comparative Clinical Pharmacology

Anastrozole, letrozole, and exemestane display differences in their pharmacokinetic and pharmacodynamic properties. Anastrozole and letrozole bind reversibly to the aromatase enzyme (and are classed as Type II nonsteroidal AIs),[24] whereas exemestane binds irreversibly, causing permanent inactivation of the aromatase enzyme, even after the drug is cleared from the circulation (and is classed as a Type I steroidal AI).[24] Steroidal and nonsteroidal AIs differ in their modes of interaction with, and inactivation of, the aromatase enzyme. Steroidal AIs compete with the endogenous ligands androstenedione and testosterone for the active site of the enzyme, where they are metabolized to intermediates that bind irreversibly to the active site, causing irreversible enzyme inhibition.

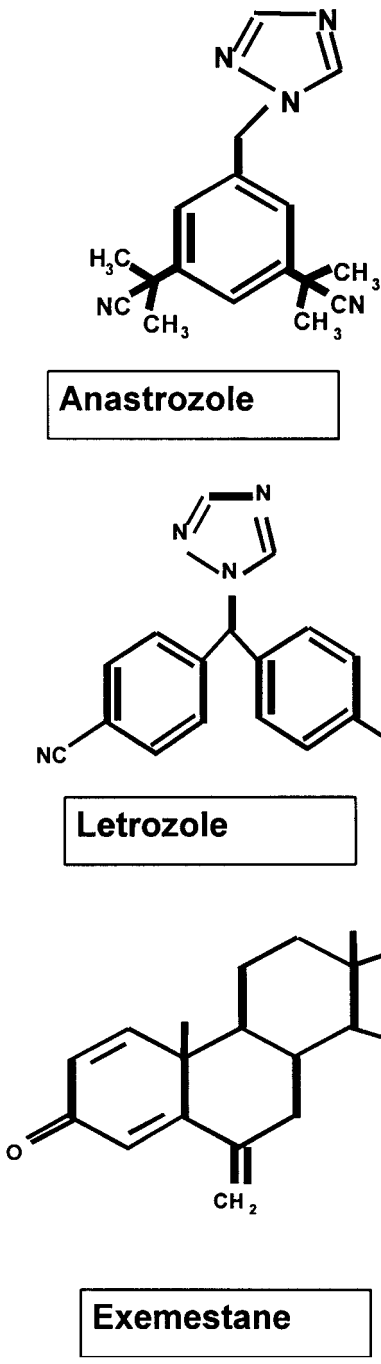

FIGURE 1. Chemical structures of the aromatase inhibitors anastrozole, letrozole, and exemestane.

Nonsteroidal AIs compete with the endogenous ligands for the active site, where they form a strong but reversible, coordinate bond to the haem iron atom to exclude both ligands and oxygen from the enzyme. Although the method by which aromatase is inhibited by both of these classes of AIs differs, both classes lead to the potent suppression of aromatase. Therefore, the clinical relevance of these differences in mechanism of action, if any, remains to be established.

TABLE 1
Clinical Pharmacology of the New-Generation Aromatase Inhibitors

Characteristic	Anastrozole	Letrozole	Exemestane
Class of AI	Type II	Type II	Type I
Daily clinical dose (mg daily)	1.0	2.5	25
Total monthly dose (mg)	30	75	750
Time to steady-state plasma levels (days)	7[a]	60[b]	7[c]
Half-life (hours)	41[d]	2–4 days[e]	27[f]
Time to maximal E_2 suppression (days)	3–4[g]	2–3[h]	7[i,j]
Suppression of plasma estrogens compared with baseline (%)			
E_2	84–85[k]	88[l]	62–65[m]
E_1	81–87[k]	84[l]	64–72[m]
E_1S	94[k]	98[l]	52[m]
Intratumoral activity reported	Yes[n]	Yes[o]	Yes[p]

AI: aromatase inhibitor; Type II: nonsteroidal aromatase inhibitor; Type I: steroidal aromatase inhibitor; E_2: estradiol; E_1: estrone; E_1S: estrone sulphate.
[a] See Camp-Sorrell.[28]
[b] See Bajetta et al.[30]
[c] See Clemett and Lamb.[28]
[d] See Yates et al.[32]
[e] See Anonymous[34] and Sioufi et al.[35]
[f] See Spinelli et al.[33]
[g] See Plourde et al.[25]
[h] See Demers et al.[26]
[i] See Zilembo et al.[27]
[j] E_2 samples were taken at 7-day intervals.
[k] See Geisler et al.[36,37]
[l] See Geisler et al.[37]
[m] See Bajetta et al.[22] and Zilembo et al.[27]
[n] See Geisler et al.[38]
[o] See Miller.[39]
[p] See Dixon et al.[40]

Anastrozole, letrozole, and exemestane each are given orally at once-daily doses of 1 mg, 2.5 mg, and 25 mg, respectively (Table 1). The time taken to reach maximal E_2 suppression for anastrozole and letrozole is 2–4 days,[25,26] compared with 7 days for exemestane.[27] However, it should be noted that Zilembo and colleagues[27] took measurements only every 7 days, and it is not known whether maximal E_2 after exemestane occurred before this. Whether these differences have any impact on the onset of therapeutic action remains to be established.

Anastrozole and exemestane both attain steady-state dosing conditions by 7 days.[28,29] In contrast, it has been reported that letrozole takes 60 days to achieve steady-state plasma levels,[30] which may be reflective of the accumulation that occurs with letrozole over long-term dosing.[31] In this study, compared with the mean letrozole concentration of 44.6 nmol/L

TABLE 2
Interactions with the Cytochrome P450 System

Anastrozole[a]	Letrozole[b]	Exemestane[c]
Inhibits CYP1A2 and CYP2C9 at relatively high concentrations	Inhibits CPY2A6 and CYP2C19	Metabolized by CPY3A4 and aldoketoreductases
No activity on CYP2A6 or CYP2D6	Metabolized by CYP3A4 and CYP2A6	—
Metabolized by N-dealkylation, hydroxylation, and glucuronidisation	—	—

[a] See Grim and Dyroffl.[41]
[b] See Wirz et al.[42]
[c] See Anonymous.[43]

reported after 14 days of letrozole treatment, there were increases of 25% (55.8 nmol/L), 29% (57.6 nmol/L), and 34% (59.7 nmol/L) in the mean plasma letrozole levels after 28 days, 56 days, and 84 days of treatment, respectively.[31] These results suggest a nonlinear relation between the dose and the efficacy of letrozole. The half-lives of anastrozole (1 mg) and exemestane (25 mg) are 41 hours[32] and 27 hours,[33] respectively, whereas it has been reported that the half-life for letrozole (2.5 mg) is up to 4 days.[34,35]

It has been established from monitoring the plasma levels of estrogen in women with breast carcinoma that AIs effectively reduce plasma E_2, estrone (E_1), and estrone sulphate (E_1S), by 81–94% for anastrozole,[36,37] 88–98% for letrozole,[37] and 52–72% for exemestane[22,27] (Table 1). Because no head-to-head trials have been carried out for all three AIs, it is not possible to conclude which of these agents is most potent with respect to E_2 suppression. However, one study that compared the extent of plasma E_1, E_1S, and E_2 suppression after 6 weeks of treatment with either anastrozole or letrozole in postmenopausal women with metastatic breast carcinoma[37] found that anastrozole and letrozole reduced plasma E_2 levels by 84.9% and 87.8%, respectively (there was no significant differences between the groups). Anastrozole and letrozole reduced E_1 levels by 81.0% and 84.3%, respectively, although the extent of this suppression was significantly greater in the letrozole group ($P = 0.019$). Anastrozole and letrozole reduced plasma E_1S levels by 93.5% and 98.0%, respectively, with the extent of this suppression significantly greater in the letrozole group compared with the anastrozole group ($P = 0.019$). Thus, although the suppression of both E_1 and E_1S after treatment with letrozole are marginally greater compared with the suppression seen after treatment with anastrozole, it is not known whether the small increase in potency seen with letrozole has any clinical impact either in terms of clinical benefit (CB) or long-term side effects from estrogen deprivation. In a separate study, it was found that exemestane treatment suppressed plasma E_2 levels compared with baseline by 65%.[27]

Direct observations of the effects of AIs on breast tissue are relatively scarce. Because some breast tumors have the capacity to synthesize estrogens using local aromatase (in situ aromatization), resulting in considerably higher concentrations of tumor estrogens compared with the concentrations seen in the circulation, it is important to show that these agents are active within the tumor. Separate studies have confirmed that anastrozole, letrozole, and exemestane all reduce tumor estrogens, but differences in the way that these data are presented make it difficult to assess whether one agent is more potent than another.[38–40] A small study by Geisler and colleagues[38] reported that, in 14 postmenopausal women with locally advanced breast carcinoma, 15 weeks of treatment with anastrozole (1 mg once daily) reduced E_2, E_1, and E_1S levels within breast tumors by 88.1%, 83%, and 73%, respectively. It was reported that 3 months of treatment with letrozole (2.5 mg once daily) significantly reduced estrogen concentrations ($P = 0.02$) in 11 postmenopausal women with hormone receptor positive breast tumors.[39] Exemestane treatment (25 mg once daily) for 3 months also reportedly reduced *profoundly* estrogen levels within breast tumors in 11 postmenopausal women with hormone receptor positive breast tumors, although the significance value was not stated.[40] Levels of the aromatase enzyme within the tumor also were reduced by anastrozole, letrozole, and exemestane, with all three agents resulting in reductions of a similar degree (97–98%).[38–40]

Comparison of Interactions with the Cytochrome p450 System and Drug-Drug Interactions

Anastrozole,[41] letrozole,[42] and exemestane[43] were evaluated separately (at concentrations of ≤ 500 μM for each drug) for pharmacokinetic activity with the cytochrome p450 system in human and rat microsomal preparations (see Table 2). Anastrozole inhibits (in decreasing order of magnitude) CYP1A2,

CYP2C8/9, and CYP3A4[41] and has no effect on CYP2A6 or CYP2D6; letrozole strongly inhibits CYP2A6 and moderately inhibits CYP2C19, and it has low affinity for CYP3A4;[42] and exemestane is metabolized by CYP3A4.[43] Thus, there is potential for drug-drug interactions if patients are prescribed concomitant medication that interacts with these cytochrome P450 enzymes. Specific interaction studies have shown that anastrozole does not interact with antipyrine (a compound used as a substrate for nonspecific P450 activity).[44] Neither anastrozole nor letrozole interact with cimetidine (a marker for CYP3A4 activity)[41,42] or warfarin (a marker for CYP3A4 and CYP1A2 activity).[41,42,45] To date, no formal drug-drug interaction studies have been reported for exemestane, although the potential for drug-drug interactions is likely to arise only for drugs that affect CYP3A4.

Tamoxifen interacts with both anastrozole and letrozole. A recent publication from the Arimidex, Tamoxifen, Alone and in Combination (ATAC) trial by the ATAC Trialists' Group[46] reported that lower plasma levels of anastrozole were observed when it was administered in combination with tamoxifen (mean decrease in the minimum plasma concentration [C_{min}] of 27%; 90%CI, 20–30%[46]). However, the same article reported that this interaction did not appear to have an impact on the E_2 suppression that is expected with anastrozole, suggesting that the interaction may have no clinical relevance. Baseline E_2 plasma levels were 21.3 pmol/L, 19.3 pmol/L, and 21.6 pmol/L prior to treatment and 3.7 pmol/L, 20.9 pmol/L, and 3.6 pmol/L after 3 months in the anastrozole, tamoxifen, and combination groups, respectively. The E_2 suppression results supported the continuation of the combination arm in the ATAC trial.

Letrozole also interacts with tamoxifen (mean decrease in C_{min} of 38%; 90%CI, 32–43%)[47] but to a greater extent compared with the interaction seen with the anastrozole-tamoxifen combination. However, the reduction in levels of letrozole in combination with tamoxifen does not appear to alter E_2 suppression by aromatase inhibition.[47] To date, there has been no opportunity to compare the clinical effectiveness of the letrozole-tamoxifen combination with either treatment alone, because the pharmacokinetic interaction between this combination meant that this treatment arm was dropped from the trial that ultimately reported the superiority of letrozole over tamoxifen.[18]

Androgenic Effects

Anastrozole and letrozole have no androgenic, progestrogenic, or estrogenic effects, such as weight gain, acne, and hypertrichosis; although they generally are associated with supratherapeutic doses, these effects have been reported in patients receiving the approved clinical doses of exemestane (Table 3).[21–23] These side effects may lead to tolerability issues, particularly if prolonged treatment is envisaged, for example, in the adjuvant setting.

Lipid Profile

Four decades of epidemiologic research in the Framingham Study have provided data to support the finding that an elevated total cholesterol (comprised of low-density lipoprotein [LDL] and high-density lipoprotein [HDL]) to HDL cholesterol ratio is an important risk factor for the development of cardiovascular disease.[48] Thus, drugs that alter lipid profiles may increase the risk of developing cardiovascular disease. A recent report from a large data set indicates that treatment with anastrozole does not markedly alter lipid profiles (compared with baseline measures); data derived from patients (n = 952 patients at study entry) who were recruited into two large advanced breast carcinoma trials comparing anastrozole and tamoxifen showed that anastrozole (1 mg once daily) did not affect nonfasting lipids in women with advanced breast carcinoma (measurements were taken every 12 weeks for $>$ 2 years).[49] Although no formal statistics were carried out, the mean baseline total cholesterol level in the anastrozole group was 5.8 mmol/L, and, after 84 weeks of treatment, there was a slight increase of + 0.3 mmol/L. For the same parameter in the tamoxifen group, the baseline level was 5.9 mmol/L at baseline, and the level decreased by 0.6 mmol/L after 84 weeks of treatment. The baseline HDL cholesterol level in the anastrozole group was 2.4 mmol/L, and the level decreased by 2.1 mmol/L after 84 weeks of treatment. In the tamoxifen group for the same parameter, the mean baseline level was 3.7 mmol/L, and the level decreased by 2.2 mmol/L after 84 weeks of treatment. The LDL level in the anastrozole group was 3.7 mmol/L at baseline, and this level increased slightly by 0.2 mmol/L after 84 weeks of treatment. In the tamoxifen group for the same parameter, the baseline LDL cholesterol level was 3.8 mmol/L, and the level decreased by 0.9 mmol/L after 84 weeks of treatment.[49] These data are supported by another smaller study in postmenopausal women (n = 44 patients) with breast carcinoma in which, compared with baseline measures, up to 32 weeks of treatment with anastrozole did not alter any lipid parameters significantly (total cholesterol, LDL and HDL cholesterol, and triglycerides; no raw values were available in the report).[50]

A preliminary study showed that, compared with baseline values, letrozole (2.5 mg once daily) had an

TABLE 3
Selectivity of the New-Generation Aromatase Inhibitors

Characteristic	Anastrozole	Letrozole	Exemestane
Androgenic properties	No[a]	No[a]	Yes[b]
Lipid profiles	No change[c]	Increase in total cholesterol, LDL, cholesterol, and apoprotein B[d]	Decrease in total and HDL cholesterol, apo A1, and total-triglyceride levels[e]
Effect on basal cortisol level	No change[f]	No change[g] or reduced ($P < 0.03$)[h]	No change[i]
Effect on basal aldosterone level	No change[f]	No change[g] or increased ($P = 0.025$)[h]	No change[i]
Effect on ACTH-stimulated cortisol synthesis	No change[f]	Reduced ($P = 0.015$)[g]	ND
Effect on ACTH-stimulated aldosterone synthesis	No change[f]	Reduced ($P = 0.04$)[g]	ND
Ratio of clinical dose to the dose-that alters cortisol or-aldosterone levels	> 10[j]	1[k]	> 32[l]
Bone resorption	NS increase, (in males age > 65 years)[m]	Increase in biomarkers (in healthy, postmenopausal women; $P < 0.05$[n] and $P < 0.005$[o])	ND

SHBG: sex hormone-binding globulin; ACTH: adenocorticotrophic hormone; ND: no data available; NS: not significant.
[a] See Michaud and Buzdar.[21]
[b] See Michaud and Buzdar,[21] Baketta et al.,[22] and Jones et al.[23]
[c] See Dewar et al.[49] and Wojtackiet al.[50]
[d] See Eliasf et al.[51]
[e] See Engan et al.[52] and Lohrisch et al.[53]
[f] See Buzdar and Esparza-Guerra.[55]
[g] See Bajetta et al.[30]
[h] See Bisagni et al.[31]
[i] See Evans et al.[57]
[j] See Buzdar and Esparza-Guerra.[55] and Wolter et al.[56]
[k] See Bajetta et al.[30] and Bisagni et al.[31]
[l] See Di Salle et al.[62]
[m] See Lai et al.[60]
[n] See Harper-Wynne et al.[61]
[o] See Heshmati et al.[59]

unfavorable effect on fasting lipids in 20 women with advanced breast carcinoma after 8 weeks and 16 weeks of treatment,[51] with letrozole treatment resulting in significant increases in total cholesterol ($P = 0.05$; mean ± standard deviation [SD] at baseline vs. 16 weeks: 239 mg/dL ± 56 mg/dL vs. 258 mg/dL ± 53 mg/dL, respectively), LDL cholesterol ($P < 0.01$; mean ± SD at baseline vs. 16 weeks: 148 mg/dL ± 50 mg/dL vs. 170 mg/dL ± 53 mg/dL, respectively), and apolipoprotein B ($P = 0.05$; mean ± SD at baseline vs. 16 weeks: 109 mg/dL ± 36 mg/dL vs. 117 mg/dL ± 32 mg/dL, respectively) levels. In addition, 9 weeks of treatment with exemestane in postmenopausal women with advanced breast carcinoma resulted in a significant decrease in total cholesterol ($P < 0.01$; mean ± SD at baseline vs. 12 weeks: 6.58 mmol/L ± 0.98 mmol/L vs. 5.74 mmol/L ± 0.79 mmol/L, respectively), HDL cholesterol ($P < 0.01$; mean ± SD at baseline vs. 12 weeks: 1.39 mmol/L ± 0.23 mmol/L vs. 0.95 mmol/L ± 0.20 mmol/L, respectively), and total triglycerides ($P = 0.023$; mean ± SD at baseline vs. 12 weeks: 1.64 mmol/L ± 0.45 mmol/L vs. 1.38 mmol/L ± 0.38 mmol/L, respectively),[52] which decreases are in a favorable direction for total cholesterol and triglycerides but in an unfavorable direction for HDL cholesterol. However, the results of a European Organization of Research and Treatment of Cancer Trial ($n = 122$ patients) showed that 24 weeks of exemestane had no impact on serum lipids.[53] Although it is difficult to extrapolate these data into the adjuvant setting, particularly because it is not known whether there will be any long-term clinical relevance in terms of cardiovascular morbidity, the results of these four studies clearly show that anastrozole, letrozole, and exemestane appear to have different effects on plasma lipids.

Adrenal Steroidogenesis

The mineralocorticoid aldosterone is involved in the regulation of blood volume and serum sodium and potassium levels; therefore, macroscopic changes in aldosterone levels ultimately can affect blood pressure control and result in disturbances of electrolyte balance. Cortisol is the major stress hormone in humans, with plasma levels rising dramatically under conditions of physical or mental stress, and it is believed generally that this rise enables humans to cope and adapt to stress. Reducing cortisol levels can result in a

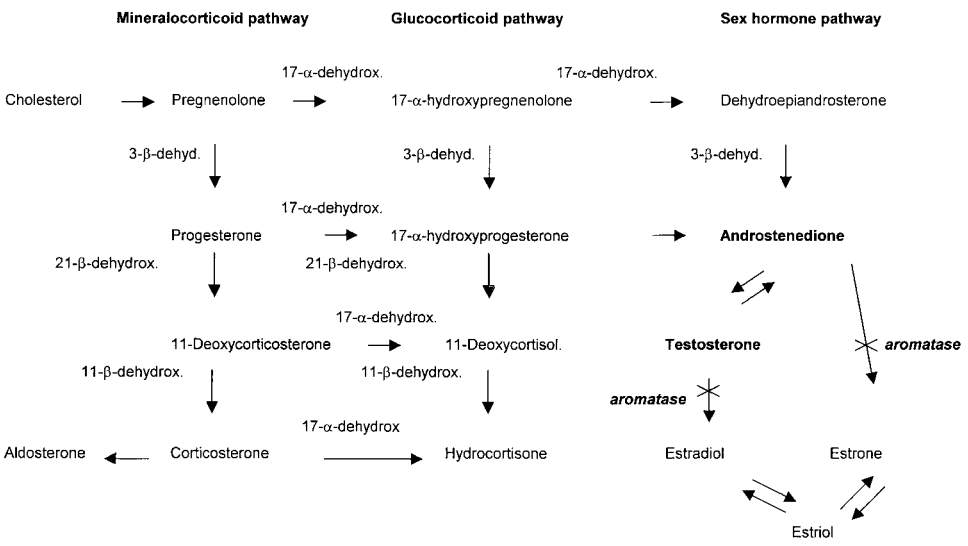

FIGURE 2. Illustration of the adrenal steroidogenesis pathway. 17-α-hydrox.: 17-α-hydroxylase; 3-β-dehy.: 3-β-dehydrogenase; 11-β-dehydrox.: 11-β-hydroxylase; 21-β-dehydrox.: 21-β-dehydroxylase.

reduced ability to withstand the impact of stress. Figure 2 illustrates the adrenal steroidogenesis pathway.

In terms of adrenal steroidogenesis, data indicate that anastrozole is the most selective nonsteroidal AI. It lacks an impact on adrenal steroidogenesis at doses up to 10 times the recommended clinical doses (Table 3), thus suggesting that anastrozole has little activity on other cytochrome P450 enzymes. The cytochrome enzyme 11-hydroxylase mediates the formation of cortisol in humans and the formation of 11-deoxycorticosterone (11-DOC) in monkeys and dogs. In preclinical studies in monkeys at a dose of 3 mg/kg, twice-daily treatment with anastrozole did not alter 11-DOC, a result that the authors suggest indicates a margin of safety for anastrozole of 30-fold.[54] In the clinical setting, basal and adrenocorticotrophic hormone (ACTH)-challenged cortisol levels of healthy postmenopausal women did not differ from baseline levels after treatment for 14 days with anastrozole (5 mg and 10 mg once daily) at doses 5-fold and 10-fold higher than the clinically administered dose (raw data not available).[54] After long-term treatment with the same doses of anastrozole, as an extension to the short-term study, there was no effect on basal (baseline levels vs. 115 days: 378 nmol/L vs. 398 nmol/L, respectively) and ACTH-stimulated cortisol (60 minutes poststimulation baseline levels vs. 115 days: 1099 nmol/L vs. 1008 nmol/L, respectively)[55] at approximately 3 months, thus further indicating a wide margin of selectivity for anastrozole.

The enzyme 18-hydroxylase, which mediates the formation of aldosterone, also does not appear to be effected by anastrozole: Preclinical studies in male rats demonstrated that plasma aldosterone levels were not affected significantly by doses of anastrozole of up to 20 mg/kg. The authors suggest that this indicates a margin of selectivity of at least 200-fold.[54] In the clinical setting, basal and ACTH-stimulated aldosterone levels (raw data not available) in healthy postmenopausal women did not differ from baseline levels after following 14 days of treatment with anastrozole (5 mg and 10 mg once daily) at doses 5-fold and 10-fold higher than the clinically administered dose.[56] In addition, long-term treatment with the same doses of anastrozole for up to 115 days in the same patients had no effect on basal (baseline levels vs. 115 days: 372 nmol/L vs. 383 nmol/L, respectively) and ACTH-stimulated (60-minute poststimulation baseline levels vs. 115 days: 901 nmol/L vs. 860 nmol/L, respectively) aldosterone.[55]

With respect to letrozole treatment, one report by Bisagni and colleagues[31] showed that basal cortisol levels and ACTH-stimulated cortisol synthesis were reduced significantly by letrozole (0.5 mg once daily) after treatment for 56 days ($P = 0.0029$; mean baseline value vs. 56 days: 188 ng/mL vs. 149 ng/mL, respectively) and treatment for 84 days ($P = 0.0006$; mean baseline value vs. 84 days: 188 ng/mL vs. 138 ng/mL, respectively) in 14 postmenopausal women with progressive, metastatic breast carcinoma. However, in the same study, it was found that letrozole had no effect on basal aldosterone levels after 84 days of treatment (at baseline vs. 84 days: 74 pg/mL vs. 58 pg/mL, respectively).[31] By contrast, more recently, Bajetta and colleagues[30] found a significant increase ($P = 0.025$) in basal aldosterone levels (raw data not available) in 46 postmenopausal women with advanced breast carcinoma after 3 months of treatment with clinical doses of letrozole of either 0.5 mg ($n = 22$ patients) or 2.5 mg ($n = 24$ patients) once daily and found a significant

decrease in ACTH-stimulated aldosterone levels after treatment with the clinically administered dose of letrozole (2.5 mg; $P = 0.04$).

There has been only one study published to date with respect to the impact of treatment with exemestane on adrenal steroidogenesis. Evans and colleagues[57] reported that exemestane administered acutely to 29 healthy postmenopausal women ($n = 3–4$ patients per group) at doses ranging from 0.5 mg to 800 mg resulted in no change in cortisol or aldosterone levels for up to 7 days after treatment (raw data not available).

Results to date show that anastrozole treatment for up to 115 days has little impact on cortisol and aldosterone levels at up to 10 times the clinical dose,[55] and one acute study with exemestane also reported no changes in these levels.[57] Treatment for up to 84 days with letrozole alters cortisol and aldosterone levels[30,31]; however, the clinical relevance of these differences has yet to be elucidated.

Bone Metabolism

Epidemiologic data have suggested a correlation between low serum estrogen levels and bone resorption in late-postmenopausal women, although a direct cause-and-effect relation has not been established. This phenomenon raises the possibility that the newer generation AIs may have adverse effects on bone by increasing resorption, and this may give rise to diseases, such as osteoporosis. To date, exemestane has been assessed only in the preclinical setting.[58] In that study, the authors randomized female rats to three groups (Group 1, ovariectomized rats that received no treatment; Group 2, ovariectomized rats that were treated with exemestane; and Group 3m intact rats that received no treatment) and measured bone mineral density (BMD) in the left femur and lumbar spine at baseline and after 16 weeks of treatment. Results showed that exemestane treatment prevented bone loss: The ovariectomized rats that received exemestane treatment had 99% of the BMD observed in the intact rats after 16 weeks of treatment, whereas the ovariectomized rats had a significantly lower BMD ($P < 0.0001$) compared with the intact rats during the same period.[58] However, whether this finding can be extrapolated to the clinical setting remains to be elucidated. Anastrozole and letrozole are the only AIs that have been investigated in the clinical setting with respect to bone resorption, and the results for both agents are shown in Table 3. One study found that six men (age > 65 years) who were treated with anastrozole (1 mg once daily) for 3 weeks had a nonsignificant increase in bone resorption (measured by N-telopeptide and C-terminal), although there was little change in bone formation (as measured by osteocalcin and bone specific alkaline phosphatase).[59] Treatment with letrozole (2.5 mg once daily) for 6 months in healthy postmenopausal women resulted in a significant increase in bone resorption, as measured by urinary pyridinoline and deoxypyridinoline, compared with baseline ($P < 0.005$ for both markers).[60] More recently, a study published by Harper-Wynne and colleagues[61] showed that 3 months of treatment with letrozole resulted in increases in bone resorption (as measured by C-terminal). In the absence of head-to-head studies with anastrozole and letrozole, it is not possible to determine whether they have any different effects on bone resorption, because the duration of treatment was different as well as the bone markers and the gender of the volunteers.

Conclusions

To date, there are no data suggesting that there are any major differences in clinical efficacy between the newer generation AIs anastrozole, letrozole, and exemestane. However, there are differences between the three agents in terms of pharmacokinetics and their effects on plasma lipids, bone, and adrenosteroidogenesis. Based on the observed pharmacologic profiles, it cannot be assumed that each of the AIs will display the same tolerability and safety profiles when they are given for extended periods of time in the adjuvant setting. The effects of anastrozole, letrozole, and exemestane are being investigated in the adjuvant setting, and these data will elucidate the possible long-term consequence of the pharmacologic effects reported after short-term exposure.

Given the differences in pharmacologic profile, the successful adoption of these agents into the treatment of patients with early-stage breast carcinoma should be based on results from the ongoing adjuvant trial programs for each of the drugs. In the absence of data, it cannot be concluded that each of the AIs will provide identical efficacy and safety profiles, and, until such data are available, it will not be possible to establish fully the benefit:risk ratio for each of these drugs.

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