

In Vivo Measurement of Aromatase Inhibition by Letrozole (CGS 20267) in Postmenopausal Patients with Breast Cancer

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ABSTRACT

Thirteen postmenopausal women with advanced breast cancer were enrolled in an open randomized Phase I trial of a new p.o. active aromatase inhibitor, CGS 20267 (letrozole). The primary aim of the trial was to assess the impact of two doses of letrozole (0.5 and 2.5 mg/day) on the peripheral aromatization of androstenedione to estrone. An *in vivo* isotopic technique was used to measure peripheral aromatization in each patient before treatment. The patients were then randomly assigned to one of the two doses, and measurements of aromatization were repeated after 6 weeks. At 0.5 mg and 2.5 mg/day, letrozole inhibited aromatization by 98.4% (97.3 to >99.1) and >98.9% (98.5 to >99.1; geometric means and ranges), respectively. Plasma estrogen levels were also measured before and during treatment. At the dose of 0.5 mg/day estrone and estradiol levels fell by 82.0% and 84.1% (geometric means), respectively. At the dose of 2.5 mg/day, the estrogens fell by 80.8% and 68.1%, respectively.

There were no significant differences between the doses in aromatase inhibition. No formal statistical analysis was performed on the estrogen data. Letrozole is therefore a highly effective inhibitor of aromatase, causing near complete inhibition of the enzyme in peripheral tissues at the doses investigated. The falls in estrogen levels were greater than those seen with earlier generation aromatase inhibitors.

INTRODUCTION

Between one-third and a one-half of breast carcinomas are dependent on estrogen for their continued growth and development. As a result of this, pharmaceutical agents which deprive the tumor of estrogenic signals are widely used. The most frequently used agent tamoxifen is thought to exert the bulk of its therapeutic effectiveness as a result of antagonism of estrogen (1). However, over the last 15 years, inhibitors of the enzyme of estrogen synthesis, aromatase, have also been found to be useful agents in breast cancer treatment. The first of these

agents, AG,² established the role of such inhibitors (2, 3), but its use is limited by its lack of specificity and its association with a number of toxic side effects (4). The only other aromatase inhibitor which is licensed is 4-hydroxyandrostenedione (formestane; Lentaron). This is more specific than AG and has few systemic side effects (5), but has poor p.o. pharmacological activity and therefore has to be given by i.m. injection (6). The associated local side effects limit the dose of formestane to one which achieves between 80 and 90% inhibition of aromatization (7).

A number of nonsteroidal inhibitors are now completing Phase III studies in advanced breast cancer. In earlier studies on one of these, letrozole (CGS 20267), we demonstrated that it was a highly potent and effective suppressant of estrogen levels in postmenopausal volunteers (single dose) and in postmenopausal patients with advanced breast cancer (8, 9). A single dose of letrozole was able to suppress estrone and estradiol levels below the detection limit of sensitive assays in many patients. In the majority of volunteers, estrogen levels did not return to baseline within 2 weeks of this single dosage. Letrozole had been shown to be highly selective *in vitro*, in rodents (10), and in clinical studies (8, 9, 11).

At the present time, there are no data directly demonstrating the effectiveness of this compound on its target enzyme. This study set out to derive these data, to allow comparison of the drug's pharmacological effectiveness with that of other compounds under development, and to assess the effectiveness of two different doses which are currently being compared in clinical Phase III studies.

PATIENTS AND METHODS

Treatment

Twelve patients were to be randomly allocated to a daily p.o. dose of 0.5 mg or 2.5 mg letrozole for a treatment period of at least 6 weeks. One of the 12 patients was replaced because the tracer injection was given without [¹⁴C]estrone. All patients were postmenopausal or had received a bilateral ovariectomy ($n = 2$). Four patients had ceased menstruation for <5 years, and one patient had a radiation menopause. In these patients, menopausal status was confirmed by the measurement of plasma gonadotrophin levels. The median age of the patients was 64 (range, 44–76) years, and the median weight was 63.7 (range, 43–79) kg. The median age for the patients treated with 0.5 mg was 49.5 (range, 44–76) years, and the median age for the 2.5-mg group was 68 (range, 45–73) years. The median

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² The abbreviations used are: AG, aminoglutethimide; CI, confidence interval.

weights for the two groups were 59.5 (range, 43–79) kg and 72.2 (range, 56–76) kg, respectively.

Patients had local regional recurrence or progressive metastatic breast cancer that had been histologically or cytologically diagnosed. Patients who were estrogen receptor-negative were excluded from treatment. Five of the patients were estrogen receptor positive, and the other eight were unknown. All patients had received previous therapy but had been off treatment for at least 4 weeks prior to the initiation of this study. Previous treatment with aromatase inhibitors was not allowed. Patients with rapidly progressive metastases, endocrine disorders, renal or hepatic dysfunction, or hematological disorders and concurrent malignant disease were excluded. The measurement of peripheral aromatization was conducted in the 4 days prior to starting therapy (from days 1–4 of the trial) and after 5½ weeks of treatment (days 43–46 of the trial). Plasma was drawn for measurement of estrone and estradiol on days 1, 4, 22, 43, and 46 and for pharmacokinetic measurement on days 22, 43, and 46.

Clinical response was not a primary end point of this study but was recorded according to standard Union International Contre Cancer criteria.

The protocol was approved by the Ethics Committee of the Royal Marsden Hospital, and each of the participants gave written informed consent. Injections of radioactive material were covered by a certificate for the "Administration of Radioactive Substances for Medicinal Purposes."

***In Vivo* Aromatization**

This methodology has been described in detail previously (12), but some minor modifications were introduced in this study to increase the sensitivity of the method, since the efficiency of inhibition of aromatization with letrozole was anticipated to be high. In brief, patients were given injections of 500 μCi [7- ^3H]androstenedione (Amersham International, United Kingdom) and 5 μCi [4- ^{14}C]estrone (New England Nuclear, United Kingdom) in a saline:ethanol mixture of 99:1. Aliquots of the isotopes in the injection mixture were taken for calculation of the ratio of $^3\text{H}:^{14}\text{C}$. All urine was collected for 72 h after injection, and the urine was then pooled, the volume was measured, and it was stored at -20°C until analysis.

Pre- and on-treatment samples were analyzed simultaneously. Two-thirds of the urine volume was concentrated on an XAD Amberlite column (Sigma, United Kingdom). Free steroids were removed on a salt gradient column packed with DEAE Sephadex (Pharmacia, Uppsala, Sweden). The eluate was enzymatically hydrolyzed with β -glucuronidase for 48 h, and androgens were then removed using a phenolic extraction method as follows. The incubate was extracted with 3×30 ml ether for 5 min, and the aqueous phase was discarded. The pooled ether fractions were washed with 10 ml 8% NaHCO_3 for 5 min. The ether was then extracted with 3×20 ml 0.1 N NaOH, and the ether was discarded. Hydrochloric acid was added to the NaOH to reduce the pH to between 2 and 4, and the solution was extracted with 2×40 ml ether. The ether extract was washed with 10 ml 8% NaHCO_3 and with 10 ml distilled water. The ether was dried down and was then available for further purification by column chromatography.

The phenolic extract was further purified on a DEAE Sephadex column and a QAE Sephadex (Pharmacia) column prior to separation of the individual estrogens by HPLC. This was conducted on a Hypersil ODS 5- μm (Chrompack) 4.6×250 -mm reverse phase column and a mobile phase of 0.05 M acetonitrile:phosphate buffer (38:62), pH 3. This technique has been shown to derive radiochemically pure estrogens (12). The fractions from the HPLC column were counted for 20 min on a TriCarb 1900 CA liquid scintillation analyzer. The $^3\text{H}:^{14}\text{C}$ ratio for each of the estrogens was calculated, and the rate of aromatization was determined by comparison to the $^3\text{H}:^{14}\text{C}$ in the injection mixture. The percentage of inhibition of aromatization on treatment was derived by comparison of the on-treatment to the pretreatment level.

The sensitivity of the modified methodology for measuring aromatase activity and its inhibition was determined by assessing the 95% counting error of zero ^3H counts in the presence of the mean number of ^{14}C counts found in the estrogen fractions. By expressing the upper limit of the 95% confidence limits for ^3H in terms of aromatase activity, the upper limit of detection of aromatase inhibition was calculated as 99.1%.

Plasma Estrogen Analyses

The RIA for estradiol has been described in detail elsewhere (13). This assay has a detection level of 3 pmol/liter.

The RIA for estrone was conducted as described by Trunet *et al.* (14). The sensitivity limit of this assay was 10 pmol/liter.

Statistical Methodology

General. The trial was designed assuming a type I error rate of 10% (*i.e.*, $\alpha = 0.10$). An 80% confidence interval was calculated for the variables described below, since the trial was designed on the basis of a one-tailed 90% test assuming that the higher dose would show a greater percentage of aromatase inhibition. Such a confidence interval reflects the design if only one limit is inspected. Geometric means rather than standard arithmetic means are quoted if a logarithmic transformation to the data was performed for analysis purposes and back-transformed for presentation purposes.

***In Vivo* Inhibition of Aromatization.** Percentage of aromatization was calculated for both pretreatment and on-treatment values for estrone and estriol individually and for their total. The percentage of inhibition was calculated for each as described above. Logarithmic transformations were made to the values calculated for percentage of inhibition. A *t* test for independent samples was performed on these to compare the values for the two dose groups. The geometric means for each dose group were calculated. The ratio for the geometric means and respective 80% confidence intervals were calculated as estimates of the difference between the dose groups in terms of percentage of inhibition. In addition, a paired *t* test was performed on the percentage of aromatization within each dose group to investigate whether a significant change occurred in their absolute values over time. Summary statistics and estimates for the changes in absolute values over time with the respective 80% confidence intervals were again calculated.

Table 1 Individual values of the aromatization rate for patients at the two doses of letrozole and the percentage of inhibition of aromatization on-treatment

Patient	Dose (mg)	Aromatization		
		Pretreatment	On-treatment	% Inhibition
2	0.5	1.547	0.042	97.3
6		1.691	0.030	98.2
7		1.416	0.011	>99.1
10		2.141	0.000	>99.1
11		1.328	0.022	98.4
1	2.5	1.211	0.019	98.4
5		1.406	0.019	98.6
8		2.362	0.009	>99.1
12		2.560	0.006	>99.1
13		2.988	0.018	>99.1

RESULTS

Two of the patients were inevaluable for *in vivo* aromatization. As stated above, one of the patients did not begin treatment after recruitment and was replaced by another randomized patient. One patient took the medication before the first tracer injection, which invalidated the pretreatment aromatization measurement.

Of the 11 evaluable patients, 6 received 0.5 mg and 5 received 2.5 mg.

Aromatase Inhibition. Table 1 shows the individual values for aromatization before and on-treatment along with the measurement of the percentage of inhibition. Pretreatment levels of aromatization varied between 1.2 and 3.0%. In two patients on 0.5 mg and three patients on 2.5 mg, the residual amount of aromatization on treatment was below the detection limit of the assay. All patients on the lower dose showed >97% inhibition and on the higher dose >98%. There were no statistically significant differences between the doses.

Plasma Estrogens. There was a marked and highly significant suppression of plasma estrone and estradiol levels by both doses of letrozole (Table 2 and Fig. 1). The pretreatment levels of both estrogens were lower for the 0.5-mg group. All values of estrone for both doses at day 43 and 46 were below the detection limit (10 pmol/liter), and the majority of the on-treatment values for estradiol were also close to the detection limit of that assay (3 pmol/liter). It is therefore difficult to express these data as a true percentage of pretreatment values. For statistical purposes, concentrations below the detection limit were given a value 1 decimal point below the respective detec-

tion limit (e.g., <10 was given a value of 9.99). Using these values by week 6, the mean suppression of estrone was 82.0% (80% CI, 79.6–84.1%) and 80.8% (80% CI, 78.3–83.1%) and of estradiol was 84.1% (80% CI, 78.3–88.3%) and 68.1% (80% CI, 54.4–77.7%) at the 0.5- and 2.5-mg doses, respectively. There was no evidence in the data suggesting any difference in the suppression of estrone and estradiol. Because so few samples were available and valid for analysis by week 6, no formal comparative statistical analysis was performed.

Clinical Response and Tolerability. Assessment of clinical response was not a primary aim of this study but was recorded at the time of the second injection (i.e., 6 weeks after starting treatment). At this stage, one of the patients was unassessable. Of the other 12, 4 of the patients were responders (one complete and three partial). Four of the patients were characterized as no change and four as having progressive disease.

The drug was well tolerated, with few adverse experiences being considered to be associated with the drug. One patient showed an increase in hot flushes which was considered to be possibly related to drug usage. No patient required discontinuation of treatment for anything other than progressive disease. There were no clinically significant changes in hematological or biochemical laboratory investigations.

DISCUSSION

Over recent years, numerous aromatase inhibitors have entered into early clinical trials. The interest in aromatase inhibitors for the treatment of estrogen-dependent diseases, or potentially the manipulation of estrogen-dependent physiological processes, was instigated by the effectiveness of AG (3). Two different types of inhibitor have since been developed: (a) steroidal substrate analogues such as 4-hydroxyandrostenedione (formestane) and exemestane and (b) nonsteroidal inhibitors which bind directly to the cytochrome P450 prosthetic group of aromatase such as rogletimide (15–17) and fadrozole hydrochloride (14, 18, 19). Most recently, a group of triazole inhibitors have been studied clinically, including letrozole, vorozole, and arimidex (8, 9, 11, 20–22).

All three of these inhibitors appear to suppress estrogen levels close to or below the detection limit of sensitive estrogen assays, but even with the most sensitive assays it has not been possible to demonstrate >80–90% suppression. It had previously been argued (23) that the use of assays based on direct measurement of aromatase activity by isotopic analysis is a more precise measurement for comparisons between drugs or

Table 2 Geometric mean levels and 80% CIs (range) of estrone and estradiol at each time point and each dose of letrozole

Treatment	Day	Estrone				Estradiol			
		0.5 mg		2.5 mg		0.5 mg		2.5 mg	
		Mean	Range	Mean	Range	Mean	Range	Mean	Range
Pre-	1	40.9	30–59	60.3	35–84	19.4	12–32	32.5	15–52
	4	44.1	33–82	67.8	54–90	21.3	13–41	23.2	16–37
On-	22	11.4	<10–17	<10.0	<10.0	4.6	<3.0–11	3.9	3.6–4.6
	43	<10.0	<10.0	<10.0	<10.0	4.0	3.4–4.7	5.2	4.9–5.6
	46	<10.0	<10.0	<10.0	<10.0	3.7	<3.0–4.3	5.9	3.7–10

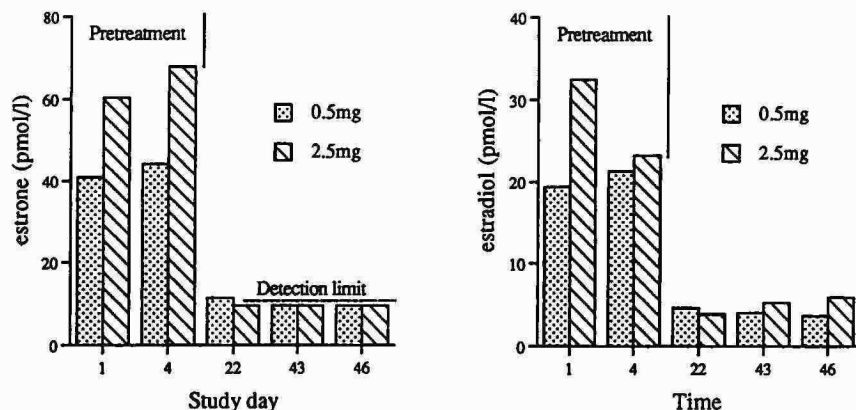


Fig. 1 Geometric mean levels of estrone and estradiol at each time point and each dose of letrozole.

dosages of the same drug. As such, we have previously demonstrated that formestane at its conventional dose of 250 mg inhibits aromatase activity between 80 and 85% (7), and fadrozole at doses of 1 or 2 mg twice a day inhibits aromatase by 82.4 or 92.6%, respectively (19). This technique also demonstrated that the use of p.o. 4-hydroxyandrostenedione or roglethimide is associated with substantially lower degrees of aromatase inhibition than this (7, 16).

Given the degree of suppression of estrogen observed with the triazole compounds (8, 9, 20), it was anticipated that letrozole would be more effective than any of the agents measured so far, and as a result of this the aromatase assay was sensitized and subjected to a formal analysis of sensitivity (99.1% inhibition). It is clear that letrozole achieves aromatase inhibition greater than any of the inhibitors that we have previously analyzed: inhibition was virtually absolute at both doses and there was no significant difference between the two doses.

The pretreatment levels of aromatase ranged between 1.2 and 3%, and these are consistent with previous measurements in postmenopausal women (7, 16, 19, 24). It is notable that the age and weight of the patients on 0.5 mg/day was lower than those on 2.5 mg, and this is consistent with the higher levels of aromatization and plasma estrogen in the 2.5-mg group at baseline. It seems unlikely that this would have significantly affected the results on percentage of inhibition, since statistically significant reduction in the percentage of aromatization was seen over time with each dose.

The inhibition of aromatase by vorozole, another triazole inhibitor, at doses of 1.0, 2.5, and 5.0 mg/day has been reported to be approximately 93–94% (25). It seems likely, however, that the sensitivity level of that analysis was insufficient to distinguish between the doses or to allow measurement to the degree of sensitivity that has been achieved in the current study. As such, comparison of letrozole with the other triazole compounds in their pharmacological effectiveness awaits the application of more sensitive assays to patients treated with these other compounds.

Although clinical efficacy and tolerability were not primary end points for this study, it was notable that 4 of the 12 patients studied showed an objective response within 6 weeks of starting treatment. Given that at least 3 months of treatment is

generally given prior to estimates being made of the clinical response, continued follow-up may have revealed further objective responders from among the patients with stable disease at 6 weeks. Our previous data on response with this agent also demonstrated a 33% response rate (9). Additionally, we previously found that tolerability of letrozole is excellent, and our experience in the present study confirmed this assessment.

Letrozole is a well-tolerated and clinically effective compound which achieves a greater degree of aromatase inhibition *in vivo* than has been previously reported for other compounds. The two doses of 0.5 and 2.5 mg appear to inhibit aromatization *in vivo* to a similar degree. There is therefore no reason to expect a higher degree of antitumor efficacy at the higher dose. The current ongoing clinical Phase III trials will demonstrate whether this is the case.

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REFERENCES

- Jordan, V. C. Biochemical pharmacology of antiestrogen action. *Pharmacol. Rev.*, 36: 245–276, 1984.
- Santen, R. J., Santner, S., Davis, B., Veldhuis, J., Samojlik, S., and Ruby, E. Aminoglutethimide inhibits extraglandular estrogen production in postmenopausal women with breast carcinoma. *J. Clin. Endocrinol. Metab.*, 47: 1257–1265, 1978.
- Stuart-Harris, R., Smith, I. E., Dowsett, M., Bozek, T., McKinna, J. A., Gazet, J.-C., Jeffcoate, S. L., Kurkure, A., and Carr, L. Low-dose aminoglutethimide in treatment of advanced breast cancer. *Lancet*, 2: 604–607, 1984.
- Stuart-Harris, R. C., and Smith, I. E. Aminoglutethimide in the treatment of advanced breast cancer. *Cancer Treat. Rev.*, 11: 189–204, 1984.
- Coombes, R. C., Hughes, S. W. M., and Dowsett M. 4-Hydroxyandrostenedione: a new treatment for postmenopausal patients with breast cancer. *Eur. J. Cancer*, 28A: 1941–1945, 1992.
- Dowsett, M., Mehta, A., King, N., Smith, I. E., Powles, T. J., Stein, R. C., and Coombes R. C. An endocrine and pharmacokinetic study of 4 oral doses of formestane in postmenopausal breast cancer patients. *Eur. J. Cancer*, 28: 415–420, 1992.
- Jones, A. L., MacNeill, F., Jacobs, S., Lonning, P. E., Dowsett, M., and Powles, T. J. The influence of intramuscular 4-hydroxyandro-

- stenedione on peripheral aromatisation in breast cancer patients. *Eur. J. Cancer*, 28: 1712–1716, 1992.
8. Iveson, T. J., Smith, I. E., Ahern, J., Smithers, D. A., Trunet, P. F., and Dowsett, M. Phase I study of the oral nonsteroidal aromatase inhibitor CGS 20267 in healthy postmenopausal women. *J. Clin. Endocrinol. Metab.*, 77: 324–331, 1993.
 9. Iveson, T. J., Smith, I. E., Ahern, J., Smithers, D. A., Trunet, P., and Dowsett, M. Phase I study of the oral non-steroidal aromatase inhibitor CGS 20267 in postmenopausal patients with breast cancer. *Cancer Res.*, 53: 266–270, 1993.
 10. Bhatnagar, A. S., Hausler, A., Schieweck, K., Lang, M., and Bowman, R. Highly selective inhibition of oestrogen biosynthesis by CGS-20267. A new non-steroidal aromatase inhibitor. *J. Steroid Biochem. Mol. Biol.*, 37: 1021–1027, 1990.
 11. Lipton, A., Demers, L. M., Harvey, H. A., Kambic, K. B., Grossberg, H., Brady, C., Aldercreuletz, H., Trunet, P. F., and Santen, R. J. Letrozole (CGS 20267)—phase I study of a new potent oral aromatase inhibitor in breast cancer. *Cancer (Phila.)*, 75: 2132–2138, 1995.
 12. Jacobs, S., Lonning, P. E., Haynes, B., Griggs, L., and Dowsett, M. Measurement of aromatization by a urine technique suitable for the evaluation of aromatization inhibitors *in vivo*. *J. Enzyme Inhibition*, 4: 315–325, 1991.
 13. Dowsett, M., Cunningham, D., Nicol, S., Lal, A., Evans, S., Brodie, A. M. H., Jeffcoate, S. L., and Coombes, R. C. Endocrinology and pharmacokinetics of oral 4-hydroxyandrostenedione treatment for postmenopausal patients with advanced breast cancer. *Steroids*, 50: 615–61, 1987.
 14. Trunet, P. F., Mueller, P. H., Girard, F., Aupetit, B., Bhatnagar, A. S., Xognbi, F., Ezzet, F., and Menard, J. The effects of fadrozole hydrochloride on aldosterone secretion in healthy male subjects. *J. Clin. Endocrinol. Metab.*, 74: 571–576, 1992.
 15. Foster, A. B., Jarman, M., Leung, C-H., Rowlands, M. G., Taylor, G. N., Plevy, R. G., and Sampson, P. Analogues of aminoglutethimide: selective inhibition of aromatase. *J. Med. Chem.*, 28: 200–204, 1985.
 16. Dowsett, M., MacNeill, F., Mehta, A., Newton, C., Haynes, B., Jones, A., Jarman, M., Lonning, P., Powles, T. J., and Coombes, R. C. Endocrine, pharmacokinetic clinical studies of the aromatase inhibitor 3-ethyl-3-(4-pyridyl) piperidine-2,6-dione (“pyridoglutethimide”) in postmenopausal breast cancer patients. *Br. J. Cancer*, 64: 887–894, 1991.
 17. MacNeill, F. A., Jones, A. L., Jacobs, S., Lonning, P. E., Powles, T. J., and Dowsett, M. The influence of aminoglutethimide and its analogue rogletimide on peripheral aromatisation in breast cancer. *Br. J. Cancer*, 66: 692–697, 1992.
 18. Dowsett, M., Stein, R. C., Mehta, A., and Coombes, R. C. Potency and selectivity of the non-steroidal aromatase inhibitor CGS 16949A in postmenopausal breast cancer patients. *Clin. Endocrinol.*, 32: 623–634, 1990.
 19. Lonning, P. E., Jacobs, S., Jones, A., Haynes, B., Powles, T. J., and Dowsett, M. The influence of CGS 16949A on peripheral aromatisation in breast cancer patients. *Br. J. Cancer*, 63: 789–793, 1991.
 20. Johnston, S. R. D., Smith, I. E., Doody, D., Jacobs, S., Robertshaw, H., and Dowsett, M. The clinical and endocrine effects of the oral aromatase inhibitor vorozole in postmenopausal patients with advanced breast cancer. *Cancer Res.*, 54: 5875–5881, 1994.
 21. Borms, M., Vandebroek, J., Rutten, J., Tytgat, J., DeCoster, R., Langenaeken, C., and Bruynseels, J. Vorozole-racemate (R76713): a specific non-steroidal aromatase inhibitor pilot study in advanced postmenopausal breast cancer (Abstract). *Eur. J. Cancer*, 29: S84, 1993.
 22. Plourde, V., Dyroff, M., and Dukes, M. Arimidex: a potent and selective fourth generation aromatase inhibitor. *Breast Cancer Res. Treat.*, 30: 103–111, 1994.
 23. Dowsett, M. Clinical development of aromatase inhibitors for the treatment of breast and prostate cancer. *J. Steroid Biochem.*, 37: 1037–1041, 1990.
 24. Grodin, J. M., Siiteri, P. K., and MacDonald, P. C. Source of estrogen production in postmenopausal women. *J. Clin. Endocrinol. Metab.*, 36: 207–214, 1973.
 25. Van der Wall, E., Donker, T. H., De Frankrijker, E., Nortier, H. W. R., Thijssen, J. H. H., and Blankenstein, M. A. Inhibition of the *in vivo* conversion of androstenedione to estrone by the aromatase inhibitor vorozole in healthy postmenopausal women. *Cancer Res.*, 53: 4563–4566, 1993.

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