

COMPARISON OF THE EFFECTS OF EM-652 (SCH57068), TAMOXIFEN, TOREMIFENE, DROLOXIFENE, IDOXIFENE, GW-5638 AND RALOXIFENE ON THE GROWTH OF HUMAN ZR-75-1 BREAST TUMORS IN NUDE MICE

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EM-652 exerts pure antiestrogenic activity in the mammary gland and endometrium, while tamoxifen, the antiestrogen most widely used for the treatment of breast cancer, exerts mixed antiestrogenic–estrogenic activity in these tissues. Our objective was to compare the agonistic and antagonistic effects of EM-652 with tamoxifen and 5 other antiestrogens on the growth of ZR-75-1 human breast xenografts in ovariectomized nude mice. During the 23 weeks of treatment at a daily oral dose of 50 µg, EM-652 was the only compound that decreased tumor size relative to pretreatment values, whereas the 6 other antiestrogens only decreased to various extents the progression rate stimulated by estrone. Under estrone stimulation, all groups of animals had more than 60% of their tumors in the progression category except for the EM-652–treated group, where only 7% of the tumors progressed. In the absence of estrone stimulation, progression was seen in 60%, 33%, 21% and 12% of tumors in the tamoxifen-, idoxifene-, toremifene- and raloxifene-treated groups, respectively, while only 4% of tumors progressed in the EM-652–treated group. The agonistic and antagonistic actions of each antiestrogen were also measured on endometrial epithelial cell thickness. Our present findings indicate that EM-652, in addition to being the most potent antiestrogen on human breast tumor growth, has no agonistic effect in breast and endometrial tissues. Since previous data have shown benefits of EM-652 on bone density and lipid profile, this compound could be an ideal candidate for chemoprevention of breast and uterine cancers, while protecting against osteoporosis and cardiovascular disease.

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Key words: breast cancer; antiestrogen; EM-652 (SCH57068); tamoxifen; toremifene; raloxifene; idoxifene; droloxifene; GW-5638; xenograft; ZR-75-1 cell; nude mouse

Breast cancer is the most frequent cancer in women, affecting 1 of every 9 women during their lifetime. Indeed, it was predicted that 192,000 new cases of breast cancer would be diagnosed in the United States in 2001, while 40,200 women were expected to die from this disease during the same time period.¹ Breast cancer is thus a major medical and public health problem.

Among all factors, estrogens are recognized as playing the predominant role in breast cancer development and growth.² It is also well known that estrogen deprivation causes regression of breast tumors. Since the first step in the action of estrogens in target tissues is binding to the estrogen receptors (ERs),^{3,4} a logical approach for the treatment of estrogen-sensitive breast cancer is the use of antiestrogens that competitively bind to ERs and block estrogen action.

Tamoxifen has been widely used over the past decades and has shown important benefits in breast cancer therapy at all stages of the disease. Unfortunately, in patients with advanced disease who initially respond, recurrence of the cancer during or after treatment is observed in most cases. The absence or loss of response to tamoxifen might be attributed to a suboptimal blockade of estrogen action or to partial agonistic activity of the compound.^{5,6} Because of these limitations of tamoxifen, major efforts have focused on the development of new antiestrogens devoid of intrinsic agonistic activity.^{7–9} Indeed, this lack or loss of inhibition by tamoxifen could be explained by its inability to block ER activation by

growth factors and other factors that act through the MAP kinase pathway at the AF-1 site of both ER α and ER β .^{10,11}

Some antiestrogens, *e.g.*, ICI-182,780 or EM-139, have also been developed from the steroidal structure of estradiol. Although these agents exhibit strong and pure antiestrogenic activity, their steroidal structure does not permit an oral formulation.¹² Orally active antiestrogens, namely, toremifene, droloxifene, idoxifene and GW-5638, have been developed as analogs of tamoxifen. EM-652 was developed originally for its pure antiestrogenic activity in the treatment of breast cancer.¹³

Our present objective was to compare the agonistic and antagonistic effects of EM-652 and 6 other oral antiestrogens selective estrogen receptor modulators (SERMs) on the growth of well-characterized, estrogen-sensitive ZR-75-1 breast cancer xenografts in ovariectomized nude mice. Previous data have shown the very high potency of EM-652 as a pure antiestrogen on the mammary gland and uterus, *in vitro* as well as *in vivo*. In brief, EM-652 is the active metabolite of the prodrugs EM-800 and EM-652 HCl, which are available in oral form. Both are potent nonsteroidal estrogen antagonists of both the α and β ER subtypes.¹⁴ It was thus of interest to develop a relevant human mammary tumor model that permits an objective comparison of the characteristics of each antiestrogen. Such a system should permit a more biologically relevant classification of each antiestrogen and provide additional information about their potential clinical benefits.

MATERIAL AND METHODS

Human ZR-75-1 breast cancer cells

ZR-75-1 human breast cancer cells were obtained from the ATCC (Rockville, MD) and cultured in phenol red-free RPMI-1640 medium. Cells were supplemented with 2 mM L-glutamine, 1 mM sodium pyruvate, 100 IU penicillin/ml, 100 µg streptomycin/ml and 10% (v/v) FBS and incubated in a humidified atmosphere of 95% air/5% CO₂ at 37°C. Cells were passaged weekly and harvested at 85–90% confluence using 0.083% pancreatin/0.3 mM EDTA.

Animals and tumor inoculation

Homozygous female *nu/nu* Br athymic mice (28–42 days old) were obtained from Charles River (Saint-Constant, Canada). Mice (5/cage) were housed in vinyl cages equipped with air filter lids,

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Received 6 August 2001; Revised 5 October 2001; Accepted 12 October 2001

DOI 10.1002/ijc.10302

which were kept in laminar airflow hoods and maintained under pathogen-limiting conditions. The photoperiod was 12 hr of light and 12 hr of darkness (lights on at 07:15). Cages, bedding and food (Agway Pro-Lab R-M-H Diet 4018, Agway Inc. C.G., Syracuse, NY) were autoclaved before use. Water was autoclaved and provided *ad libitum*. Bilateral ovariectomy was performed under isoflurane-induced anesthesia. At the time of ovariectomy, an implant of estradiol (E_2) was inserted s.c. to stimulate initial tumor growth. E_2 implants were prepared in 1 cm long Silastic tubing (inside diameter 0.062 inch, outside diameter 0.095 inch) containing 0.5 cm of a 1:10 (w/w) mixture of E_2 and cholesterol. One week after ovariectomy, 2×10^6 ZR-75-1 (passage 93) cells were inoculated s.c. in 0.1 ml of RPMI-1640 medium + 30% Matrigel on both flanks of each ovariectomized (OVX) mouse through a 2.5 cm long 22-gauge needle. After 4 weeks, E_2 implants were replaced in all animals by estrone-containing implants of the same size (E_1 :chol, 1:25, w:w). Randomization and treatments were started 1 week later.

Treatments

One day prior to initiation of treatments, 255 mice bearing ZR-75-1 tumors of an average area of $24.4 \pm 0.4 \text{ mm}^2$ (range 5.7–50.7 mm^2) were randomly assigned to 17 groups (with respect to tumor size), each containing 15 mice (total of 29 or 30 tumors). The 17 groups included 2 control groups (OVX and OVX + estrone), 7 groups supplemented with an estrone implant and treated with an antiestrogen and 8 other groups that received an antiestrogen alone. Estrone implants were then removed from animals in the OVX control group and in groups that were to receive the antiestrogen alone. Estrone-containing implants in the 8 other groups were changed thereafter every 6 weeks. EM-652, raloxifene, droloxifene, idoxifene and GW-5638 were synthesized in the medicinal chemistry division of the Oncology and Molecular Endocrinology Research Center. Tamoxifen was purchased from Plantex (Netanya, Israel), while toremifene citrate was purchased from Orion (Espoo, Finland). Under estrone stimulation, antiestrogens were given at a daily oral dose of 50 μg (2 mg/kg on average) suspended in 0.2 ml of 0.4% (w/v) methylcellulose. In the absence of estrone stimulation, animals were treated with 200 μg (8 mg/kg on average) of each antiestrogen once daily by the oral route. Animals in both control groups received 0.2 ml of the vehicle alone. Antiestrogen suspensions at the appropriate concentration were prepared each month, stored at 4°C and used under constant agitation. Powder stock was hermetically stored at 4°C (idoxifene, raloxifene, toremifene, GW-5638, droloxifene) or at room temperature (tamoxifen, EM-652).

Tumor measurements and necropsy

Two perpendicular diameters were recorded and tumor area (mm^2) was calculated using the formula $L/2 \times W/2 \times \pi$. The area measured on the first day of treatment was taken as 100%.

After 161 days of treatment, the remaining animals were anesthetized with isoflurane and killed by exsanguination. To further characterize the effect of the estrogen and antiestrogens, estrogen-responsive tissues, such as the uterus and vagina, were immediately removed, freed from connective and adipose tissue and weighed. Uteri were prepared to evaluate endometrial thickness by image analysis performed with Image Pro-Plus (Media Cybernetics, Silver Spring, MD). In brief, uteri were fixed in 10% formalin and embedded in paraffin. Hematoxylin and eosin-stained sections of uteri were analyzed. Four images/uterus (2/uterine horn) were analyzed. Mean epithelial cell height was measured in all animals of each group.

Response criteria

Tumor response was assessed at the end of the study or at the death of each animal, if it occurred during the course of the experiment. In this case, only data of mice that survived for at least half of the study (84 days) were used in the tumor response

analysis. In brief, *complete regression* identifies those tumors that were undetectable at the end of the experiment, *partial regression* corresponds to tumors that regressed to 50% or less of their original size, *stable response* refers to tumors that regressed <50% or progressed <50% and *progression* refers to tumors that progressed $\geq 50\%$ compared to their original size.

Statistical analyses

The change in total tumor surface area between days 1 and 161 was analyzed by ANOVA for repeated measurements. The model included treatment, time and time-treatment interaction effects plus a term to account for the strata at randomization. The significance of the different treatment effects at 161 days was thus tested by the time-treatment interaction. Analysis of the residuals indicated that measurements on the original scale were not fitted for ANOVA or any of the transformations that were tried. Therefore, ranks were selected for the analyses. The effect of the treatments on epithelial thickness was assessed by a 1-way ANOVA, including the strata at randomization. *A posteriori* pairwise comparisons were performed using least-square means. The overall Type I error rate (α) was controlled at 5% to declare significance of differences. All calculations were performed using Proc MIXED on the SAS (Cary, NC) software.

RESULTS

Antagonistic effects on ZR-75-1 tumor growth

Estrone alone (OVX+ E_1) caused a 707% increase in ZR-75-1 tumor size during the 23-week treatment period (Fig. 1a). Administration of the antiestrogen EM-652 at a daily oral dose of 50 μg to estrone-stimulated mice completely prevented tumor growth. Indeed, not only was tumor growth prevented but after 23 weeks of treatment tumor size was 26% less than the value at the start of treatment ($p < 0.04$). This value obtained after treatment with EM-652 was not statistically different from that observed after OVX alone, when tumor size decreased by 61% below the initial value. At the same dose (50 μg) and treatment period, the 6 other antiestrogens did not decrease initial average tumor size. Tumors in these groups were significantly higher than in the OVX control group and the EM-652-treated group ($p < 0.01$). Indeed, compared to pretreatment values, 23 weeks of treatment with droloxifene, toremifene, GW-5638, raloxifene, tamoxifen or idoxifene led to average tumor size increases of 478%, 230%, 227%, 191%, 87% and 86% above pretreatment values, respectively (Fig. 1a).

Agonistic effects on ZR-75-1 tumor growth

After 161 days of treatment with a daily dose of 200 μg of tamoxifen, in the absence of estrone supplementation, average tumor size increased to 196% over baseline ($p < 0.01$ vs. OVX) (Fig. 1b). However, the average tumor size of mice treated with idoxifene increased 125% ($p < 0.01$), while that in mice treated with toremifene increased by 86% ($p < 0.01$) (Fig. 1b). Addition of 200 μg of EM-652 to 200 μg of tamoxifen completely inhibited the proliferation observed with tamoxifen alone (Fig. 1c). However, treatment with EM-652 ($p = 0.44$), raloxifene ($p = 0.11$), droloxifene ($p = 0.36$) or GW-5638 ($p = 0.17$) alone did not significantly change ZR-75-1 tumor size compared to the OVX control group at the end of the experiment. (Fig. 1b).

Effects on categories of response

Effects of 50 μg antiestrogen on estrone stimulation. In addition to the effect on tumor size, the category of response achieved by each individual tumor at the end of the experiment was an important parameter of treatment efficacy. In OVX mice, complete, partial and stable responses were achieved in 21%, 43% and 38% of tumors, respectively and none of the tumors progressed. However, in OVX animals supplemented with estrone, 100% of tumors progressed (Fig. 2a). In the EM-652-treated group of OVX animals supplemented with estrone, complete, partial and stable re-

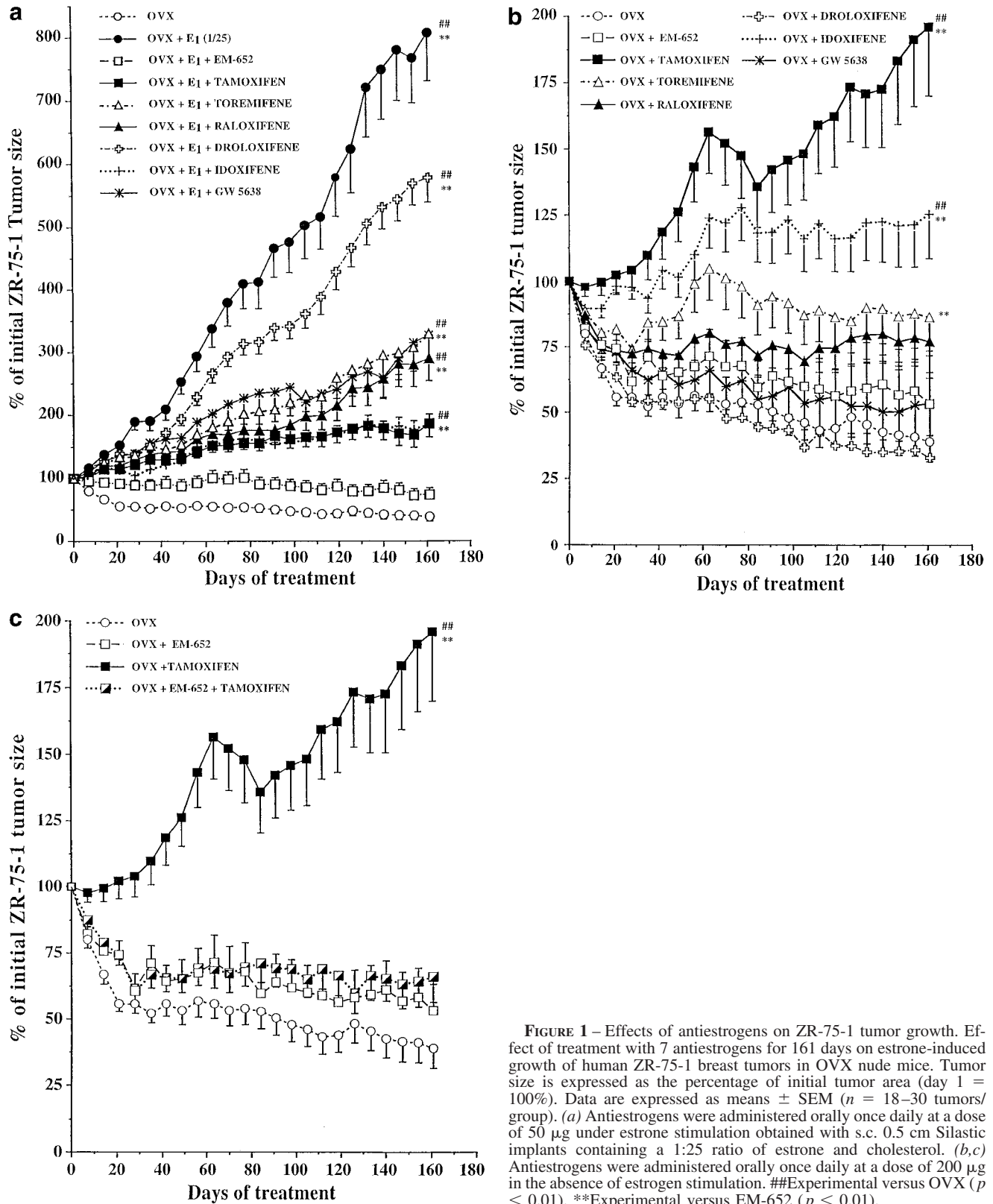


FIGURE 1 – Effects of antiestrogens on ZR-75-1 tumor growth. Effect of treatment with 7 antiestrogens for 161 days on estrone-induced growth of human ZR-75-1 breast tumors in OVX nude mice. Tumor size is expressed as the percentage of initial tumor area (day 1 = 100%). Data are expressed as means \pm SEM ($n = 18$ –30 tumors/group). (a) Antiestrogens were administered orally once daily at a dose of 50 μ g under estrone stimulation obtained with s.c. 0.5 cm Silastic implants containing a 1:25 ratio of estrone and cholesterol. (b,c) Antiestrogens were administered orally once daily at a dose of 200 μ g in the absence of estrogen stimulation. ##Experimental versus OVX ($p < 0.01$). **Experimental versus EM-652 ($p < 0.01$).

sponses were seen in 17%, 17% and 60% of tumors, respectively and only 7% (2 of 30 tumors) progressed. Under the same conditions of estrone stimulation, treatment with a daily 50 μ g dose of any of the other antiestrogens was unable to decrease the percentage of progressing tumors under 60%. Indeed, 65% of tumors (17

of 26) progressed in the tamoxifen-treated group, while 89% (25 of 28) progressed with toremifene, 81% progressed (21 of 26) with raloxifene, 100% (23 of 23) progressed with droloxifene, 71% (20 of 28) progressed with idoxifene and 77% (20 of 26) progressed with GW-5638 (Fig. 2a).

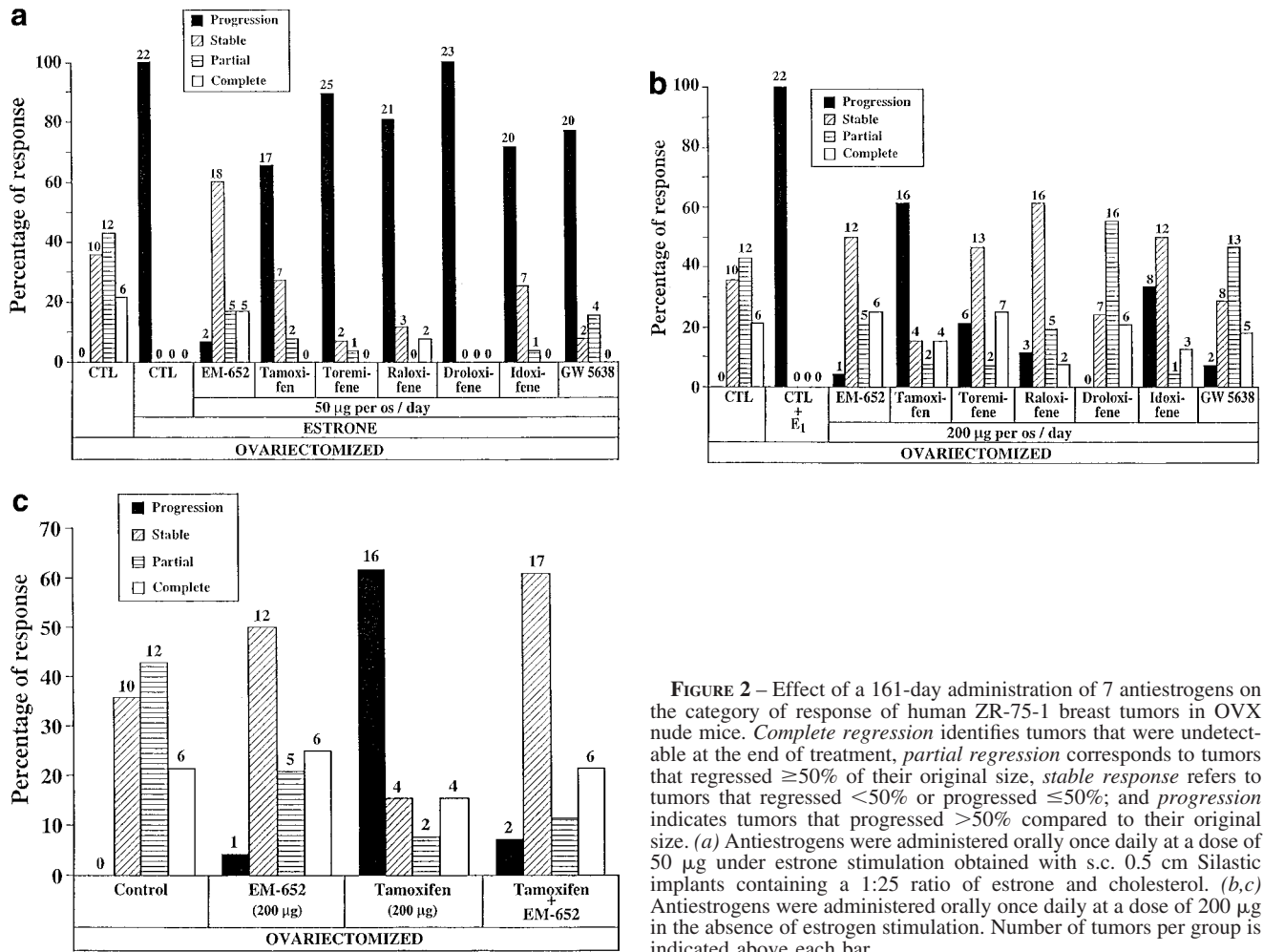


FIGURE 2 – Effect of a 161-day administration of 7 antiestrogens on the category of response of human ZR-75-1 breast tumors in OVX nude mice. *Complete regression* identifies tumors that were undetectable at the end of treatment, *partial regression* corresponds to tumors that regressed $\geq 50\%$ of their original size, *stable response* refers to tumors that regressed $< 50\%$ or progressed $\leq 50\%$; and *progression* indicates tumors that progressed $> 50\%$ compared to their original size. (a) Antiestrogens were administered orally once daily at a dose of 50 µg under estrone stimulation obtained with s.c. 0.5 cm Silastic implants containing a 1:25 ratio of estrone and cholesterol. (b,c) Antiestrogens were administered orally once daily at a dose of 200 µg in the absence of estrogen stimulation. Number of tumors per group is indicated above each bar.

Effects of 200 µg antiestrogen in the absence of estrone stimulation. As illustrated in Figure 2b, tamoxifen and toremifene led to a greater proportion of progressing tumors in the absence of estrone stimulation than the other antiestrogens. Indeed, 62% (16 of 26), 33% (8 of 24) and 21% (6 of 28) of tumors were in the progression category after tamoxifen, idoxifene and toremifene treatment at a daily dose of 200 µg, respectively. As can be seen in Figure 2c, addition of 200 µg of EM-652 to tamoxifen reduced the percentage of progressing tumors with tamoxifen alone from 62% (16 of 26) to 7% (2 of 28).

Effects of antiestrogens on thickness of uterine epithelial cells

Endometrial epithelial cell height was measured as the most direct parameter of the agonistic and antagonistic effects of each compound in the endometrium.

Effect of daily 50 µg antiestrogen in the presence of estrone stimulation. At the daily oral dose of 50 µg, EM-652 inhibited the stimulatory effect of estrone on epithelial height by 70%. The efficacy of the 6 other antiestrogens tested was significantly lower ($p < 0.01$). Indeed, droloxifene, GW-5638, raloxifene, tamoxifen, toremifene and idoxifene inhibited estrone stimulation by 17%, 24%, 26%, 32%, 41% and 50%, respectively (Table I).

Effect of daily 200 µg antiestrogen in the absence of estrone stimulation. In the absence of estrone stimulation, EM-652 and droloxifene were the only compounds tested that did not significantly increase the height of epithelial cells (114% and 101% of the OVX control group value, respectively). Tamoxifen (155%), toremifene (135%) and idoxifene (176%) exerted significant stim-

TABLE I – EFFECTS OF ANTIESTROGEN ON THICKNESS OF UTERINE EPITHELIAL CELLS

Group	Number	Endometrial epithelium thickness µm ± SEM
OVX control	14	18.31 ± 0.04
OVX + E ₁ control	8	40.58 ^{2,4} ± 0.63
OVX + E ₁ + EM-652	14	25.06 ² ± 0.07
OVX + E ₁ + tamoxifen	10	33.44 ^{2,4} ± 0.04
OVX + E ₁ + toremifene	13	31.47 ^{2,4} ± 0.04
OVX + E ₁ + raloxifene	12	34.72 ^{2,4} ± 0.06
OVX + E ₁ + droloxifene	12	36.71 ^{2,4} ± 0.12
OVX + E ₁ + idoxifene	12	29.35 ^{2,4} ± 0.05
OVX + E ₁ + GW-5638	12	35.30 ^{2,4} ± 0.07
OVX + EM-652	12	20.79 ± 0.10
OVX + tamoxifen	11	28.47 ^{2,4} ± 0.05
OVX + EM-652 + tamoxifen	13	27.95 ^{2,4} ± 0.06
OVX + toremifene	13	24.75 ^{2,3} ± 0.04
OVX + raloxifene	12	22.33 ¹ ± 0.05
OVX + droloxifene	13	18.50 ± 0.07
OVX + idoxifene	11	32.14 ^{2,4} ± 0.05
OVX + GW-5638	13	22.22 ¹ ± 0.05

Effect of 161 days of treatment with 7 antiestrogens in OVX nude mice. Results are presented as means ± SEM ($n = 8-14$). Effect of 50 µg of antiestrogens under estrone stimulation or 200 µg of antiestrogens alone on thickness of uterine epithelial cells.¹⁻² Experimental vs. OVX control mice: ¹ $p < 0.05$, ² $p < 0.01$.^{3,4} Experimental vs. EM-652-treated mice: ³ $p < 0.05$, ⁴ $p < 0.01$.

ulation of uterine epithelial height ($p < 0.01$ vs. OVX control group). Raloxifene (122%) and GW 5638 (121%) also exerted a statistically significant stimulation of uterine epithelial height ($p < 0.05$ vs. OVX control group) (Table I). The agonistic and antagonistic effects of each antiestrogen measured on uterine and vaginal weight were in accordance with the pattern observed for uterine epithelium thickness (data not shown).

DISCUSSION

Since the clinical data indicate that continuous tamoxifen therapy for 5 years is preferable to shorter-term use¹⁵ and that long-term administration prevents breast cancer,¹⁶ it is important to make available a pure antiestrogen to avoid the risks of endometrial cancer. Due to its lack of intrinsic estrogenic activity, such a compound should be more efficient than tamoxifen at preventing and treating breast cancer while simultaneously eliminating the risk of developing uterine carcinoma during long-term use. The ideal strategy for the development of new antiestrogens thus appears to rely on 3 main parameters: pure antiestrogenic activity in the mammary gland, absence of uterine stimulation and estrogen-like action on bone and lipids.^{9,17}

Toremifene, idoxifene, droloxifene and GW-5638 are 4 tamoxifen-derived compounds, developed with the objective of a greater antagonistic effect than tamoxifen on breast cancer while being less estrogenic in the uterus. These compounds, however, exert a stimulatory effect on the uterus comparable to that observed with tamoxifen.^{18–24} When toremifene was compared to tamoxifen in adjuvant trials, the results at 3 years of median follow-up showed no significant difference in breast cancer recurrence rates and adverse events in the 2 treatment arms.²⁵ Idoxifene, similarly, resulted in a similar inhibition of E_2 -dependent MCF-7 xenografts growth compared to tamoxifen.²⁶

Droloxifene and GW-5638 are less agonistic than tamoxifen at the ER.^{19,22} The small effects observed with droloxifene in the present study could be due to its low affinity for ER. In addition to these antiestrogens derived from the tamoxifen structure, raloxifene is a nonsteroidal benzothiophene derivative that has been classified as a SERM because of its antiestrogenic effects in the uterus and breast as well as its estrogen-like effects on bone and cholesterol. Raloxifene has an antagonistic effect on the rat mammary gland comparable to that of tamoxifen but appears to be less agonistic on the uterus.^{27,28} The effects of all of these antiestrogens have not been compared in the same *in vivo* experiment. Moreover, the new compound EM-652 has been found to be the most potent antiestrogen so far developed and should thus be compared to these other compounds.

Droloxifene, toremifene and ICI-182,780 have already been compared to EM-652 for their effect on breast cancer cell proliferation.²⁹ EM-652 was found to be more potent at inhibiting the proliferation of T-47D and MCF-7 cells induced by E_2 than the 3 other antiestrogens. EM-652 is 20 times more potent than ICI-182,780 or droloxifene and is 400 times more potent than toremifene at displacing E_2 from the rat uterine ER. Indeed, EM-652 has the highest known affinity for the ER when studied in competition receptor assays.³⁰ Preclinical studies have shown that EM-652 blocks *ras*-mediated induction of ER transcriptional activity in both the presence and the absence of estrogens.¹¹ Furthermore, previous data have compared EM-800 to tamoxifen on the growth of ZR-75-1 tumor xenografts in the presence or absence of estrone stimulation.³¹ In that study, EM-800 was found to be more potent than tamoxifen at inhibiting tumor growth and could reverse the stimulatory effect of tamoxifen.

EM-800 has been administered to women who had failed tamoxifen therapy. Forty-three postmenopausal or OVX women of a

median age of 67 years (43–86 years) with breast cancer resistant to tamoxifen were treated with daily oral doses of 20 or 40 mg of EM-800. One patient had a complete response and is still responding at 27 months of follow-up, while 5 patients had a partial response. Complete and partial responses have thus been observed so far in 6 patients (13.9%), while no change for at least 3 months has been observed in 13 patients (30.2%), for a total of 19 positive responses out of 43 evaluable patients (44.2%).³⁰

In agreement with the early clinical data, the present study shows greater efficacy of EM-652 on human breast cancer xenograft growth as well as pure antagonistic effects on human breast tumors and mouse endometrial thickness.

The present study has the advantage of comparing 7 antiestrogens under the same experimental conditions. Tamoxifen, idoxifene, raloxifene, toremifene and GW-5638 show comparable effects as inhibitors of estrone-stimulated human breast cancer growth in nude mice, by inhibiting estrone stimulation by 60–80%. In our study, droloxifene inhibited estrone stimulation by only 30%. Using the same parameter, EM-652 produced the greatest inhibition of tumor size or 95% inhibition of estrone stimulation.

The difference in the antiestrogenic potency between EM-652 and the other antiestrogens was also remarkable when considering the individual categories of response achieved. These results are in agreement with previous data obtained with EM-800 in the same model.³¹

In the absence of estrogen, the stimulatory effect of tamoxifen, toremifene and idoxifene was illustrated by the observation that 21–62% of the tumors progressed in these 3 groups. However, EM-652 was the only compound to show both a decrease of mean tumor size below its original value despite estrone stimulation and the absence of agonistic effect on tumor growth even if administered at a high daily dose of 200 μ g.

The height of endometrial epithelial cells is a highly sensitive estrogen-responsive parameter. In agreement with the observations on human breast tumors, tamoxifen, toremifene, raloxifene, droloxifene, idoxifene and GW-5638 had a similar inhibitory effect on the thickness of estrone-stimulated uterine epithelial cells. The inhibition of the estrogenic stimulation achieved with all of these antiestrogens was significantly lower than that observed with EM-652. Moreover, in the absence of estrone stimulation, EM-652 and droloxifene were the only antiestrogens that did not stimulate the height of endometrial epithelium cells. All of the other antiestrogens significantly increased the epithelial thickness of the endometrium.

A new strategy to fight breast cancer is chemoprevention with an antiestrogen.^{32–38} Tamoxifen and raloxifene have shown promising preventive effects and comparison of the 2 compounds has just started in large-scale clinical studies.^{16,35,39} The ideal compound for prevention of breast and uterine cancers is theoretically the one with the highest antagonistic effect and no agonistic or estrogen-like action in breast and uterine tissue while protecting against bone loss and cardiovascular disease. The active metabolite EM-652 has been shown to be the closest to the definition of the perfect antiestrogen.^{9,17} Indeed, EM-652 is a pure antagonist on breast tumor development and growth and its effect is the most potent of all of the antiestrogens tested;^{30,40} EM-652 has no stimulatory effect on the uterus and is more potent at protecting against bone loss than raloxifene.⁴¹ Moreover, EM-652 has shown very potent effects on the prevention of dimethylbenz[*a*]anthracene-induced mammary tumor development in the rat.⁴²

Based on the present study and previous data, we suggest that EM-652 could well be an ideal candidate for breast cancer prevention and treatment.

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