Topical Testosterone for Breast Cancer Patients with Vaginal Atrophy Related to Aromatase Inhibitors: A Phase I/II Study

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Evaluate early data regarding the impact of daily vaginal testosterone on estradiol and testosterone levels in breast cancer patients receiving treatment with aromatase inhibitors.
2. Explain the potential clinical benefits of vaginal testosterone therapy to treat vaginal atrophy in women with breast cancer receiving long-term aromatase inhibitor therapy.

This article is available for continuing medical education credit at CME.TheOncologist.com.

ABSTRACT

Purpose. Controversy exists about whether vaginal estrogens interfere with the efficacy of aromatase inhibitors (AIs) in breast cancer patients. With the greater incidence of vaginal atrophy in patients on AIs, a safe

and effective nonestrogen therapy is necessary. We hypothesized that vaginal testosterone cream could safely treat vaginal atrophy in women on AIs.

Methods. Twenty-one postmenopausal breast cancer

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patients on AIs with symptoms of vaginal atrophy were treated with testosterone cream applied to the vaginal epithelium daily for 28 days. Ten women received a dose of 300 μg , 10 received 150 μg , and one was not evaluable. Estradiol levels, testosterone levels, symptoms of vaginal atrophy, and gynecologic examinations with pH and vaginal cytology were compared before and after therapy.

Results. Estradiol levels remained suppressed after treatment to <8 pg/mL. Mean total symptom scores improved from 2.0 to 0.7 after treatment ($p < .001$) and remained improved 1 month thereafter ($p = .003$). Dys-

pareunia ($p = .0014$) and vaginal dryness ($p < .001$) improved. The median vaginal pH decreased from 5.5 to 5.0 ($p = .028$). The median maturation index rose from 20% to 40% ($p < .001$). Although improvement in total symptom score was similar for both doses (-1.3 for 300 μg , -0.8 for 150 μg ; $p = .37$), only the 300- μg dose was associated with improved pH and maturation values.

Conclusions. A 4-week course of vaginal testosterone was associated with improved signs and symptoms of vaginal atrophy related to AI therapy without increasing estradiol or testosterone levels. Longer-term trials are warranted. *The Oncologist* 2011;16:424–431

INTRODUCTION

Aromatase inhibitors (AIs) increase the frequency and complicate the treatment of vaginal atrophy in breast cancer patients [1, 2]. Suppression of estradiol levels by AIs alters the vaginal epithelium, rendering it drier, thinner, and less elastic. In the Arimidex, Tamoxifen, Alone or in Combination trial, vaginal dryness was observed in 16.3% and dyspareunia was observed in 17.8% of anastrozole-treated patients, but in only 8.4% and 7.5% of tamoxifen-treated patients, respectively [2]. As AIs are used more frequently in the growing population of postmenopausal women with hormone receptor-positive breast cancer, this serious complication of therapy that dramatically affects quality of life will become more common [3].

Treatment of vaginal atrophy in women on AIs is controversial. The most effective treatment for this condition is local estrogens [4]. Although neither topical estrogen creams nor vaginal estrogen tablets raise estrogen to premenopausal levels, several reports suggest that they may compromise the suppression of estrogen by AIs, theoretically putting the patient at higher risk for breast cancer recurrence [5]. In 2006, Kendall and colleagues found elevated estradiol levels in six of seven women on AIs treated with β -estradiol tablets or cream [6]. Mean serum estradiol levels were ≤ 5 pmol/L (≤ 1.36 pg/mL) before treatment, rose to a maximum of 72 pmol/L (19.6 pg/mL) at 2 weeks, and remained elevated for several months in some patients. A subsequent trial found a greater rise in estradiol in patients using an estradiol tablet than in those using a vaginal estradiol ring [7]. These small studies presented only short-term follow-up results and no data on breast cancer outcomes, yet many patients and physicians are avoiding all estrogen therapy in this setting.

Alternatives to topical estrogens include vaginal moisturizers such as Replens® (Lil' Drug Store Products,

Inc., Cedar Rapids, IA) and lubricants such as K-Y® jelly (Johnson & Johnson Inc., New Brunswick, NJ). These are often useful, but are generally not as effective as estrogen [4]. Replens® improves vaginal moisture and elasticity and restores pH; however, as a bioadhesive gel it does not reverse the cytologic effects of atrophy. Cytologic studies show improvement in cell size but no improvement in maturation values [3, 8–10]. Anecdotal reports in the online breast cancer community have suggested that testosterone might have clinical efficacy. Testosterone induces proliferation of the vaginal epithelium, and because its conversion to estrogen is blocked by AIs, we hypothesized that topical testosterone would reverse the atrophic changes of estrogen suppression without interfering with the activity of the AI [11–14].

In this study, we sought to determine the impact of vaginal testosterone on estradiol levels and, secondarily, on pathological and clinical measures of vaginal atrophy in women with breast cancer on long-term AI therapy.

METHODS

Design

In this phase I/II pilot study, we assessed whether a 28-day trial of daily vaginal testosterone affected estradiol and testosterone levels in breast cancer patients on AIs. We then evaluated whether testosterone could improve the symptoms and signs of vaginal atrophy. Finally, a dose reduction was planned if symptom improvement was noted at the initial dose.

Testosterone cream was prepared by a specialty compounding using testosterone United States Pharmacopeia micronized powder made into a paste with polysorbate 80 National Formulary (NF) liquid in an emollient cream base. The first 10 patients received a dose of 300 μg of testosterone whereas the second 10 patients were given a dose of 150 μg . The 300- μg dose was compounded with 13.5 mg

and the 150- μ g dose was compounded with 6.75 mg of testosterone propionate in 0.45 mL of polysorbate NF liquid and sufficient emollient cream base to make 45 g total. A calibrated vaginal applicator was supplied to measure out daily doses of 1 g each. The cream was applied daily for 28 consecutive days. A 300- μ g daily dose approximates the transdermal testosterone dose given to women with hypoactive sexual desire and is much lower than the dose given to men with low androgen states [15–17]. Because approximately 10% of transdermal testosterone is absorbed systemically, this dose was considered unlikely to raise serum androgen levels above normal female values [18, 19]. Even if androgen levels were elevated, serum estrogen levels were not expected to increase in the context of aromatase inhibition.

Before starting the intervention, patients received instruction on how to apply the cream using a diagram of the perineum. They were instructed to apply a portion of the cream to the inner labia minora and external vaginal mucosa digitally and the remainder of the cream to the inner vaginal mucosa digitally or with the applicator. They were instructed not to apply the cream to the clitoris, the labia majora, or any nonintact skin to avoid irritation. Patients were prohibited from using local therapies, including topical estrogen or vaginal lubricants.

Setting and Patients

Twenty-one breast cancer patients were enrolled from the medical oncology clinics of Fletcher Allen Health Care and Memorial Hospital of Rhode Island between December 2006 and October 2009. Patients were recruited if they had reported vaginal symptoms to their providers. Charts were also reviewed to identify breast cancer patients on AIs and providers were asked to question patients about symptoms of vaginal atrophy. Patients were eligible if they were undergoing primary or adjuvant treatment with an AI for a histologically or cytologically confirmed breast cancer and reported vaginal itching, dryness, or dyspareunia. Only postmenopausal patients with a life expectancy >2 months and an Eastern Cooperative Oncology Group (ECOG) performance status score ≤ 3 were eligible [20]. Postmenopausal status was defined as the absence of menses for ≥ 12 months or a follicle-stimulating hormone level >25 mIU/mL. Patients undergoing active chemotherapy or radiotherapy or on medications intended to suppress ovarian function were not eligible. Patients using vaginal estrogen within the preceding 2 months were not eligible. The study was approved by the institutional review board of each institution before patients were enrolled. Written informed consent meeting all federal, state, and institutional guidelines was obtained from all patients.

Measurements

High-sensitivity assays for estradiol were done at baseline and after 4 weeks of treatment. If post-treatment levels were elevated, they were repeated 4 weeks after treatment was completed. The assay used extraction and radioimmunoassay plus chromatography to detect changes in plasma estradiol of 1–5 pg/mL [21–24]. The analyst was blind to the identity of the patient and to whether samples were obtained before or after treatment.

Patients completed symptom questionnaires at baseline, at the end of the 4-week treatment and 4 weeks later at an 8-week follow-up visit. The questionnaire was adapted from previous studies of estrogen therapy for vaginal atrophy [25–27]. The patient was asked to rate the severity of “dryness of the vagina,” “itching or irritation of the vagina or vulva,” and “pain with intercourse” on a four-point scale (0, none; 1, mild; 2, moderate; 3, severe). Scores for all three symptoms were summed for a total symptom score. Possible scores were in the range of 0–12, or 0–8 for patients who rated dyspareunia as “not applicable” because of a lack of sexual activity.

Before and after the study intervention, a gynecologic examination was performed by one of three providers who, though not blinded to intervention status, performed independent assessments before starting therapy and within 72 hours of its completion. These included examination of the external genitalia, a speculum vaginal examination, and a pH measurement. Samples of vaginal epithelial cells were obtained with vaginal brushing. Microscopic evaluation of the vaginal epithelium was performed by one pathologist who was blinded to the identity of the patient and to whether samples were obtained before or after treatment. The maturation index was calculated from vaginal cytology using the Kupperman index [28].

Side effects were monitored throughout the study, including local reactions such as rash or pruritis, as well as hirsutism, acne, thrombosis, headache, depression, and systemic rash.

Hematocrit, liver function tests, lipid panels, and testosterone levels were obtained on all patients before and after therapy. Elevated levels were retested 1 month after therapy was completed.

Statistical Methods

The primary endpoint was maintenance of estradiol suppression. We considered any serum estradiol level in the normal postmenopausal range of ≥ 20 pmol/mL to indicate loss of aromatase inhibition. Estradiol levels were compared before and after the intervention using the Wilcoxon signed rank test [29]. An interim analysis was performed after the 10 patients on the 300- μ g dose completed therapy

Table 1. Pretreatment patient characteristics by topical testosterone dose

Characteristic	150 μ g (n = 10)	300 μ g (n = 10)	p-value
Mean age (range), yrs	57 (47–66)	56 (45–69)	.82
Total symptom score ^a ($\pm$ standard deviation)	6.2 ($\pm$ 1.48)	5.5 ($\pm$ 2.27)	.72
Dyspareunia score, median	3	3	.26
Dryness score, median	2	2	.79
Itching score, median	1	1	.94
pH, median	5.5	5	.17
Maturation index, % mature	20%	0%	.17
Median estradiol, pg/mL ^b	0	0	>.99
Median testosterone, pg/mL ^b	19	0	.037

^aSymptoms: 1, mild; 2, moderate; 3, severe.
^bEstradiol <5 pg/mL and testosterone <5 ng/dL considered equal to 0.

to confirm estradiol suppression after therapy and to assess for symptom improvement prior to implementing the 150- μ g dose of testosterone.

The secondary endpoint of clinical effect was analyzed based on serial questionnaire results. Improvement in symptom scores was calculated using the total scores for each patient and for each individual symptom using the Wilcoxon signed rank test. Power was calculated using the two-sided hypothesis that testosterone cream affects the symptoms of vaginal atrophy. We sought to detect differences in the symptom scores of at least 0.4 points on a 0–3 scale. For the effect of treatment, assuming a standard deviation of 0.5 with a two-sided $\alpha = 0.05$ and a paired comparison, a sample size of 16 subjects has 89% power. To accommodate the loss of power anticipated from using non-parametric tests, we sought 20 patients. For comparisons between the two dosing levels, the analysis is unpaired. Therefore we were only powered to detect a difference of 0.6 points in the symptom score.

The secondary endpoint of pathologic improvement of vaginal atrophy was analyzed based on a comparison of baseline and post-treatment maturation index, pH, and clinical examination. Maturation indices were compared using the Wilcoxon signed rank test [18]. The maturation index is a score of 0–100 based on the ratio of parabasal, intermediate, and superficial squamous cells, with a score <50 signifying atrophy. Studies of topical estrogen therapies typically show an improvement in the maturation index from in the 40s to in the 60s, with an increase in maturation

index ≥ 10 . We thus considered an improvement in the maturation index ≥ 10 to be significant. A drop in vaginal pH from >5 to <5 correlates with the presence and resolution of vaginal atrophy [30, 31]. Pretreatment and post-treatment values were compared using the Wilcoxon signed rank test.

RESULTS

Patients

Twenty-one women were enrolled between June 2007 and September 2009. One patient declined treatment after giving consent and was not included in the analysis. Twenty patients received treatment as planned. One patient missed the end-of-4-weeks visit and two missed the 8-week follow-up visit (4 weeks post-therapy). Patients' ages were in the range of 45–69 years. All had early-stage breast cancer. The AIs used were primarily nonsteroidal imidazole compounds—10 women were on anastrozole, whereas eight were on letrozole, and two were on the steroidal AI exemestane. Baseline estradiol levels were low, as expected during AI therapy (the highest value was 6.9 pg/mL and the remainder were ≤ 5 pg/mL) (Table 1). All women had moderate to severe symptoms of vaginal atrophy at baseline, with the most common symptom being vaginal dryness and the least common being vaginal itching. Patients on the 150- μ g and 300- μ g testosterone doses had similar baseline symptom scores, vaginal pH, and maturation indices (Table 1).

Hormone Levels

Serum estradiol levels remained low after therapy—18 were undetectable (<5 pg/mL), one was 7 pg/mL, and one was 7.6 pg/mL. There was no significant difference in median serum estradiol level before and after treatment ($p = .91$) and no difference in post-treatment estradiol levels between dosing levels ($p > .99$) (Table 2). Pretreatment serum testosterone levels were <21 ng/dL in all patients. The level rose to 113 ng/dL in one patient, and was ≤ 42 ng/dL in the others (Table 2).

Symptom Scores

Baseline complaints of dyspareunia were rated severe by 16 of 20 women (80%). Eight women rated vaginal dryness as severe and three complained of severe itching or irritation. Women had the option to mark “not applicable” instead of rating dyspareunia. All women rated this numerically at baseline, but four women marked “not applicable” at subsequent visits (Table 2).

The mean total symptom score was 2.0 at baseline, fell to 0.7 after treatment ($p < .001$), and remained low 1

Table 2. Comparison of baseline, end-of-4-week-treatment, and 8-week follow-up results for the 150- μ g and 300- μ g testosterone doses

Outcome	Baseline	4 wks post-treatment	<i>p</i> -value versus baseline	8-wk follow-up	<i>p</i> -value versus baseline
Sample size	20	19		18	
Total symptom score ($\pm$ standard deviation)	5.9 ($\pm$ 1.9)	2.1 ($\pm$ 1.77)	<.001	1	.003
Dyspareunia ^a	3	1	.001	2	.003
Dryness score, median	2	0	<.001	1.5	.017
Itching score, median	1	1	.049	0	.14
Vaginal pH, median	5.5	5.0	.028	—	
Maturation index, %	20	40	<.001	—	
Median estradiol, pg/mL	0	0	.91	—	
Median testosterone, ng/dL	15.5	21.5	.022	—	

^aSample size for dyspareunia was 14 post-treatment and 15 at 4-week follow-up.

month post-therapy ($p = .003$). The severity of dyspareunia and vaginal dryness improved significantly after treatment, but itching did not (Table 2). One month after completion of treatment, a smaller degree of improvement persisted, again significant only for dyspareunia and vaginal dryness (Table 2). There was no significant difference in the improvement seen between the 300- μ g and 150- μ g dose cohorts (Table 2).

Gynecologic Examinations, Cytology, and pH

Seventeen women completed pretreatment and post-treatment vaginal examinations. Maturation values rose from a median pretreatment value of 20% to a post-treatment value of 40% ($p < 0.001$) (Figs. 1 and 2). The mean pH level improved from 5.24 to 4.93 ($p = .028$). Clinical examination revealed post-treatment improvement in signs of atrophy, including a greater degree of lubrication, color change from white to pink, and appearance of rugae not present on the baseline examination in some patients.

Effect of Dose

The difference in improvement of clinical symptoms between high- and low-dose testosterone was not significant for the mean total symptom score (-1.3 versus -0.8 ; $p = .37$) or for individual symptoms of vaginal dryness (-2.0 versus -1.5 ; $p = .9$), vaginal itching (0 versus 0; $p = .33$), or dyspareunia (-2.0 versus -1.5 ; $p = .13$) (Table 2). Both doses demonstrated significant improvements in dyspareunia and total symptoms compared with baseline.

The change in the pathologic measurement of improvement did appear to differ by dose. Post-treatment maturation values were significantly different by dose, with a 60% higher maturation index with the 300- μ g dose and a 20%

Figure 1. Vaginal cytology from a patient before and after treatment with 300 μ g testosterone cream for 28 days. (A): Pretreatment vaginal cytology—sparse, atrophic, parabasal cells. 400 $\times$ magnification, Papanicolaou stain. (B): Post-treatment vaginal cytology—mix of mature intermediate and superficial squamous cells. 400 $\times$ magnification, Papanicolaou stain.

Figure 2. Pretreatment and post-treatment pathology results by dose level. (A): Change in maturation index (%). (B): Change in pH.

higher maturation index with the 150- μ g dose ($p = .005$) (Fig. 2B). Furthermore, nine of the 10 women on the 300- μ g testosterone dose demonstrated an increase in maturation value to $>50\%$ whereas none of the women on the 150- μ g dose did (Fig. 2B).

A significant decrease in pH compared with baseline was seen in patients on the 300- μ g dose (5.1 to 4.6), but not in patients on the 150- μ g dose (5.4 to 5.5). Comparing these two groups suggested that improvement in pH after treatment favored the 300- μ g dose over the 150- μ g dose, although this was not significant (0 versus -0.5 ; $p = .09$) (Fig. 2B).

Toxicity

Specific complaints likely related to testosterone included mild symptoms of abnormal hair growth ($n = 2$), acne ($n = 1$), vaginal rash ($n = 1$), and pruritis ($n = 1$) and moderate symptoms of vaginal discharge ($n = 1$). One month post-therapy, one woman noted a nonvaginal rash. Symptoms that improved during therapy included acne ($n = 1$), depression ($n = 2$), and vaginal and thigh “burning” ($n = 1$). One woman had an elevation in alanine aminotransferase to ECOG grade 1 that tran-

siently increased to grade 2 after treatment [17]. No elevations in hematocrit or cholesterol levels were observed. No patients stopped therapy because of side effects.

DISCUSSION

Twenty-eight days of topical testosterone was associated with improved symptoms of vaginal atrophy in 20 women on AIs without raising estradiol levels. Clinical improvement waned but was not lost 1 month after therapy. The treatment was well tolerated. This is an important finding because vaginal atrophy is common among patients on AI therapy and current treatment strategies are either ineffective or pose potential risks.

The literature on the use of topical testosterone by women on AIs is limited. Recent reports support the use of androgens and testosterone in women with vaginal atrophy and research is ongoing into the effectiveness of pilocarpine, a nonselective muscarinic receptor agonist [32–36]. A recently completed trial of intravaginal dehydroepiandrosterone (Prasterone) showed an effect on vaginal atrophy without elevation of estradiol or testosterone above usual postmenopausal levels [37]. Preliminary results from one study of vaginal testosterone in women on AIs are available [30]. Testosterone was applied at a dose of 500 μ g daily for 2 weeks then three times per week for 10 weeks, which improved vaginal atrophy and sexual function. This supports our result on the clinical effectiveness of testosterone. However, modest elevations in estradiol were noted in some patients, even after treatment ceased. This underscores the importance of finding the lowest effective dose of testosterone in this population.

The lowest effective dose of testosterone is also important for its effect on serum testosterone levels. Although the association between testosterone therapy and elevated serum testosterone levels on initial and recurrent breast cancer risk is controversial, the elevation in testosterone levels in several patients in this study is concerning. The most significant increase in serum testosterone occurred in our first patient. Modifications in the application of the cream mediated levels and subsequent patients had either no or small increases in serum testosterone. Several studies suggest that a possible greater breast cancer risk associated with testosterone is indirectly mediated by greater conversion to estrogen. This would theoretically not occur in the presence of aromatase inhibition; however, other studies suggest that this effect is mediated directly by testosterone, which would not be countered by aromatase inhibition. Observational and case-control studies reviewing the association of higher levels of serum testosterone with more frequent and recurrent breast cancer diagnoses are conflicting [38–44].

Testosterone prescribed for low libido is associated with a higher risk for an initial breast cancer diagnosis in some, but not all, studies [45, 46]. Data on testosterone levels in patients on AIs are lacking. Thus, it is prudent to closely monitor the effects of this treatment on serum testosterone in future studies of testosterone in this population.

The main limitation of this study is the lack of concurrent controls, which leaves our findings vulnerable to regression to the mean. The recruitment of subjects was not systematic, which may limit the generalization of this small sample of patients to other populations. Without concurrent controls, it is also not possible to judge how much effect was related to the cream base as opposed to the testosterone alone. Future studies will be randomized with a control arm of the cream or Replens® moisturizer.

One of the strengths of our study is the consistency of findings across a variety of measurements. Although the self-reported symptoms are subjective, they are supported by the pathologic improvement seen in the blinded comparison of vaginal cytology. The pathologic correlates of pH and the maturation index only improved significantly in the cohort on 300 μ g testosterone. Interestingly, despite the lack of a pathologic response at the lower dose, there was no difference in symptom outcomes at the different doses of testosterone studied. Given the equivalent effect on symptoms, use of the lower dose may be prudent. Alternatively, the effect of the higher dose on the thinness

of the vaginal epithelium may be associated with greater effectiveness, similar to the difference between symptom improvement with topical estrogens, which reverse the cytologic changes of vaginal atrophy, and with Replens, which does not [8].

Our findings are preliminary and require confirmation in controlled studies before clinical recommendations can be made. The doses in this study, however, provide a reasonable starting point for further testing because we were able to demonstrate clinical efficacy and tolerance in this small cohort of subjects.

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