SEXUAL MEDICINE ORIGINAL RESEARCH

Improvements to the Vulva, Vestibule, Urethral Meatus, and Vagina in Women Treated With Ospemifene for Moderate to Severe Dyspareunia: A Prospective Vulvoscopic Pilot Study

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ABSTRACT

Introduction: Ospemifene, an oral selective estrogen receptor modulator approved for the treatment of mild to moderate dyspareunia from menopause, has been shown to moderate sexual pain and vaginal epithelial cell characteristics. However, no prospective vulvoscopic studies have been performed.

Aim: To examine, in menopausal women taking ospemifene 60 mg daily, changes to the vulva, vestibule, urethral meatus, and vaginal region over 20 weeks using vulvoscopy in a prospective open-label pilot study.

Methods: Vulvoscopic photographs taken at screening and the end of therapy assessed for changes in the appearance of the vulva, vestibule, urethral meatus, and vagina rated by a single reviewer using a 10-parameter Likert rating scale, the Vulvoscopic Genital Tissue Appearance Scale (VGTA). In addition, the cotton-tipped swab test and subject diary scores were assessed over the 20-week treatment period and compared before and after the intervention using Wilcoxon signed-rank test.

Main Outcome Measure: Changes in VGTA score from baseline to end of study.

Results: 8 subjects (age = 59 ± 4.7 years) completed all visits and were included in the analysis of vulvoscopic photographs (n = 258). There were significant changes during the study period for urethral meatal prominence, introital stenosis, vestibular pallor, vestibular erythema, mucosal moisture, vaginal rugation, and anterior wall prominence ($P < .05$). Total pain score during cotton-tipped swab testing decreased from 11 (interquartile range = 10−16) before the intervention to 1 (interquartile range = 0−3) at the end of the study. Quantitative diary analysis indicated an increase in the number of sexual events, decrease in rates of pain during foreplay and intercourse, and decrease in use of lubricant at study completion ($P < .05$).

Conclusions: Ospemifene 60 mg daily for 20 weeks showed improvement in physical examination findings in this prospective study of menopausal women with dyspareunia, as documented on vulvoscopic photography. These changes were consistent with improvements in subject-reported pain and sexual function. **Goldstein SW, Winter AG, Goldstein I. Improvements to the Vulva, Vestibule, Urethral Meatus, and Vagina in Women Treated With Ospemifene for Moderate to Severe Dyspareunia: A Prospective Vulvoscopic Pilot Study. Sex Med 2018;X:XXX−XXX.**

Key Words: Vulva; Vestibule; Urethral meatus; Ospemifene; Vulvoscopy; Dyspareunia

INTRODUCTION

Ospemifene is an oral estrogen agonist and antagonist and a selective estrogen receptor modulator (SERM).[1] It is indicated for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, from menopause.[1]

It is estimated that within 1 to 6 years after menopause 64% to 85% of women will experience vulvar and vaginal atrophy,[2] currently called genitourinary syndrome of menopause (GSM).[3] GSM represents signs and symptoms associated with decreased hormone levels in menopause that can adversely affect such tissues as the labia majora, labia minora, vestibule, clitoris,

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vagina, urethra, urethral meatus, bladder, pelvic floor muscles, and periurethral anterior vaginal wall prostate tissue.[3] With an average age of onset of menopause of 51 years,[4] most women born from 1946 to 1964, the Baby Boomer generation, are menopausal. Because the life expectancy of women in the United States is approximately 80 years, women can expect to spend approximately 1/3 of their lives in menopause.[5]

A common bothersome symptom of women with GSM is painful intercourse, or dyspareunia, experienced by 2/3 of women in the 1st year of menopause.[6,7] Dyspareunia is chronic and progressive and unlikely to resolve spontaneously.[3,8] Adverse changes to the vagina in GSM that play a role in dyspareunia include shortening and narrowing of the vaginal lumen, loss of rugae in the vaginal epithelium, pallor and dryness of the vaginal mucosa, a decrease in vaginal epithelial superficial cells, an increase in vaginal epithelial parabasal cells, and an increase in vaginal pH.[9] Ospemifene is considered safe and efficacious for the treatment of dyspareunia from menopause.[10–12] In double-blinded, placebo-controlled studies, ospemifene at week 12 significantly increased superficial cells (10.8% vs 2.7% for placebo), significantly decreased parabasal cells (−34.4% vs +5.84% for placebo), significantly decreased vaginal pH (−0.97% vs −0.002% for placebo), and significantly lowered the dyspareunia severity score compared with placebo ($P = 0.0012$).[12] There also are non-vaginal genitourinary tissue adverse changes associated with dyspareunia including erythema of minor vestibular glands; fissures at the posterior fourchette; labia minora resorption; protrusion, tenderness, and prolapse of the urethral meatus; and atrophy of the clitoris.[3]

A publication of 2 case studies of long-term use of ospemifene in a clinical setting showed on presentation continued disease of the vestibule.[13] Another publication of a 60-day open-label clinical trial to examine changes in vestibular innervation used photography and a visual analog pain scale that showed that the vestibule was effectively treated with ospemifene, which also improved genitourinary tissue health in the region.[14] To better understand the role of ospemifene as an effective oral agent in the broader construct of vaginally and non-vaginally based genitourinary tissue changes, we conducted a pilot study prospectively assessing changes in vulvoscopic appearance of multiple tissues of the genitourinary system before and after 20 weeks of treatment with ospemifene.

METHODS

This was an open-label pilot study conducted at a single research center under approval of an independent review board. The primary purpose of the study was to evaluate visible vulvoscopic changes by comparing baseline with the end of the study at 20 weeks in the vulva, vestibule, clitoris, urethral meatus, and vaginal and periurethral anterior vaginal wall regions in women with moderate to severe dyspareunia treated with oral ospemifene 60 mg daily. There was no placebo arm in this pilot study. The secondary objectives were to assess for changes in pain noted with the cotton-tipped swab (Q-tip [Unilever NV, Rotterdam, The Netherlands] testing in the vestibule) and changes in sexual function as recorded in the subject diary. After signing consent, subjects who met the inclusion and exclusion criteria (Table 1) were enrolled.

Vulvoscopy is a procedure that allows a health care provider to perform a detailed examination of the vulva, vestibule, clitoris, urethral meatus, vagina, and periurethral anterior wall prostate using a vulvoscope to magnify the area 4 to 40 times and to take multiple photographs.[15] For each subject, a standardized method of optically magnified vulvoscopic examination with photography performed from lateral to medial and from external to internal was used to maximize diagnostic information.[15,16] The vulvoscope was a Wallach ZoomScope vulvoscope (Wallach Surgical Devices, Trumbull, CT, USA) with an attached foot-pedal–controlled Cannon EOS XSi Digital SLR camera

Table 1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Written informed consent	Hypersensitivity to ingredients
Female	Previously used ospemifene
Age 21–80 y	Suspected breast cancer, history of heart attack or stroke
BMI < 37 kg/m^2	Clinically significant findings at physical examination
Menopausal	Uncontrolled hypertension
Has moderate to severe dyspareunia	Chronic medical condition or psychologic disorder
Has moderate to severe pain at cotton-tipped swab testing	Using local or systemic androgen therapy
Agrees to comply with study procedures	Using local or systemic estrogen therapy
	Using a SERM
	Using itraconazole, ketoconazole, digitalis, alkaloids heparin, strong cytochrome P450 3A4 inhibitors
	History of substance abuse
	Received investigational drug within 30 d
	Behavior indicating unlikely to be compliant

BMI = body mass index; SERM = selective estrogen receptor modulator.