Ospemifene May Not Treat Vulvar Atrophy: A Report of Two Cases

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ABSTRACT

Introduction: Ospemifene (Osphena, Shionogi Inc, Florham, NJ, USA) is an estrogen agonist and antagonist approved by the U.S. Federal Drug Administration for the treatment of "moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause." Although published, peer-reviewed, placebo-controlled studies have shown objective improvement in dyspareunia and in vaginal atrophy, there are no published data that have assessed changes in vulvar atrophy after the use of ospemifene.

Aim: To present two cases of women with severe vulvar atrophy that showed no improvement with the use of ospemifene.

Methods: A review of two recent cases of a clinic specializing in the treatment of vulvovaginal disorders was performed. Case 1 was a 53-year-old menopausal woman who presented with non-provoked vulvar and vaginal discomfort and introital dyspareunia. She had used ospemifene 60 mg/d for 1.5 years without improvement in her symptoms before presentation. Case 2 was a 57-year-old menopausal woman who also presented with non-provoked vulvar rawness, burning, irritation, vaginal dryness, and introital dyspareunia. She had started ospemifene 60 mg/d 1 year before presentation and reported mild improvement in her vaginal dryness but no improvement in her vulvar irritation or introital dyspareunia.

Main Outcome Measures: Change in vulvar atrophy and introital dyspareunia.

Conclusion: These cases highlight the need to perform additional clinical trials that specifically assess the efficacy of ospemifene for changes in vulvar atrophy.

Key Words: Ospemifene; Genitourinary Syndrome of Menopause; Vulvovaginal Atrophy; Menopause

INTRODUCTION

Ospemifene (Osphena; Shionogi Inc, Florham NJ, USA) is a selective estrogen-receptor modulator that has been approved by the Food and Drug Administration for the treatment of moderate to severe vulvar and vaginal atrophy and moderate to severe dyspareunia (a symptom of vulvovaginal atrophy) with a suggested dosage of 60 mg once daily.[1] The prescribing guidelines for ospemifene are based on two 12-week, double-blinded, placebo-controlled, parallel-group efficacy trials and one double-blinded, placebo-controlled, parallel-group, 52-week long-term safety trial.

The first clinical trial was a 12-week, double-blinded, placebo-controlled, parallel-group efficacy trial that included 826 menopausal women in three randomized groups.[1,2] The first group received ospemifene 30 mg/d for 12 weeks (n = 282), the second group received ospemifene 60 mg/d for 12 weeks (n = 276), and the third group received a placebo (n = 268). The co-primary end points included the mean change from baseline in vaginal dryness or dyspareunia as indicated on a four-point scoring system, with participants stratified and assessed by the symptoms that were most bothersome at baseline (none = 0, mild = 1, moderate = 2, severe = 3) as taken at the screening appointment and again at weeks 4 and 12. Vaginal dryness was further assessed by the percentage of superficial cells and parabasal cells and vaginal pH as seen on a vaginal culture wet mount. The results of the trial indicated that women who received ospemifene in the two strata showed an improvement from baseline in vaginal dryness or dyspareunia by the four-point scale and an improvement in total Female Sexual Function Index score that was evident at week 4 and increased in magnitude until week 12.

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The second clinical trial was a 12-week, double-blinded, placebo-controlled, parallel-group efficacy and safety trial that included 919 generally healthy postmenopausal women diagnosed with vulvovaginal atrophy who had greater than or equal to 5% superficial cells on vaginal smear and a vaginal pH higher than 5.0.[1,3] The participants were stratified into two groups based on the symptoms they designated as most bothersome at baseline; the first group included those who were most bothered by vaginal dryness (dryness cohort) and the second group included those who were most bothered by pain with intercourse (dyspareunia cohort). Treatment groups included those who received ospemifene 60 mg/d for 12 weeks (n = 463) and those who received a placebo (n = 456). The co-primary end points included the mean change from baseline in their most bothersome symptoms, which were vulvar and/or vaginal dryness (combined as one variable) and dyspareunia as indicated on a four-point scoring system. Secondary end points included change from baseline in the domains of the Female Sexual Function Index as taken at weeks 4 and 12 and change from baseline in serum sex hormone levels (follicle-stimulating hormone, luteinizing hormone, and SHBG) collected at the screening appointment and at week 12. The results of this trial showed that significantly more women who reported dyspareunia as their most bothersome symptom had improvement (68.3% vs 54.1%; $P = .0255$) or relief (57.5% vs 41.8%; $P = .0205$) in the severity of their dyspareunia from baseline compared with week 12 with ospemifene use vs placebo. Participants with vulvar and/or vaginal dryness also had improvement (74.6% vs 57.7%; $P = .0101$), substantial improvement (42.4% vs 26.9%; $P = .0172$), and even relief (66.1% vs 49.0%; $P = .0140$) of their vulvar and/or vaginal dryness from baseline to week 12 with ospemifene use compared with placebo.

The third clinical trial was a 52-week, double-blinded, placebo-controlled, parallel-group extension safety trial that was conducted in 301 women 40 to 80 years old without a uterus who were recruited from the 12-week efficacy study.[4] The total elapsed time for patients was 68 weeks, including the initial 12-week study, the extension of 52 weeks, and a post-trial follow-up after 4 weeks. Women continued the 60-mg/d ospemifene dose or switched from the blinded placebo or 30-mg/d ospemifene dose to the open-label 60-mg/d ospemifene dose. Safety assessments included adverse events, laboratory studies, physical and gynecologic examination, vital signs, breast palpation, and mammography. Ospemifene was found to be clinically safe and generally well tolerated in postmenopausal patients with dyspareunia.

The two efficacy studies included an objective assessment of vaginal atrophy, However, somewhat surprisingly, ospemifene had been approved for (and is currently being marketed as) a treatment for vaginal and vulvar atrophy, although none of the published trials included any objective assessment of the vulvar tissue. Examples of tests that could have been included are quantitative sensory testing and changes in mucosal thickness as measured by biopsy examinations before and after treatment.

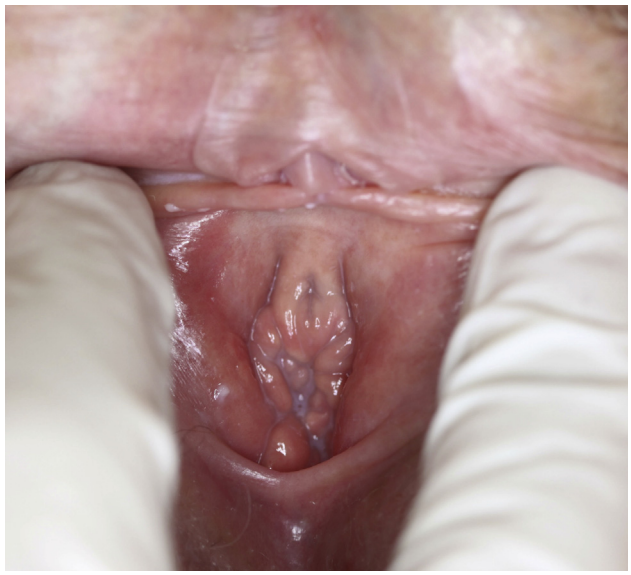

Figure 1. Severe atrophy of vulvar vestibule of a patient taking ospemifene.

This report describes two cases of postmenopausal women who used ospemifene for at least 1 year and found no improvement in vulvar atrophy or introital allodynia.

CASE 1

The patient was a 53-year-old gravida 1, para 2, aborta 0 menopausal woman who presented to a clinic specializing in the treatment of vulvovaginal disorders with complaints of non-provoked vulvar and vaginal rawness and pain with intercourse that she described as burning pain upon penetration. She reported that her symptoms had become progressively worse during the past 5 years. She had been menopausal for 10 years and had pain-free intercourse with normal lubrication and sexual arousal before the past 5 years. She had tried an estradiol vaginal ring and estradiol intravaginal tablets, without improvement in her symptoms. For the past 1.5 years, she had been taking ospemifene 60 md/d, without improvement in her symptoms. On physical examination, the patient had profound atrophy, erythema—especially of the major and minor vestibular gland ostia—and severe tenderness of the vulvar vestibule (Figure 1). There was no evidence of vulvar dermatoses. The vaginal mucosa was mildly atrophic and non-tender, without ulcerations or erosions. The bladder and urethra were non-tender to palpation. The levator ani muscles were not significantly tight or tender. The vaginal pH was 5.0, and a saline wet mount showed predominantly mature squamous cells with few leukocytes and few parabasal cells.