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EDITORIAL

Ospemifene for vulvar and vaginal atrophy: an overview

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Abstract

The menopause-related decline in estrogen levels leads to an array of genital, sexual, and urinary symptoms collectively known as genitourinary syndrome of menopause. The constellation of symptoms associated with vulvar and vaginal atrophy (VVA) can have a profoundly detrimental effect on a woman's sexual function, relationships, and quality of life. Ospemifene is a selective estrogen receptor modulator indicated for treatment of moderate-to-severe symptomatic VVA in postmenopausal women who are not candidates for local vaginal estrogen therapy or have contraindications for estrogen products. Ospemifene is administered orally, thus avoiding the inconveniences of local therapy, and can be used in women with VVA and a history of breast cancer after completing all (including adjuvant) breast cancer treatment. As well as restoring vaginal health in symptomatic VVA, ospemifene may have collateral benefits of importance to postmenopausal women. In this Special Issue entitled "Treatment of Vulvar and Vaginal Atrophy: Clinical Experience with Ospemifene," illustrative case studies examine the experiences of women with VVA during treatment with ospemifene. Specific topics include the effects of ospemifene on bone markers; its use in breast cancer survivors and in women with dyslipidemia, urinary incontinence, or VVA-related sexual dysfunction; and its concomitant use with laser therapy.

Keywords: genitourinary syndrome of menopause, ospemifene, selective estrogen receptor modulators, vulvar and vaginal atrophy.

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The lower genital and urinary tracts in women are richly endowed with estrogen receptors that maintain the thickness and moisture of the mucosa.[1] The hypoestrogenism associated with menopause leads to physiological, histological, and anatomical changes in urogenital tissues, including thinning of the vaginal epithelium; decreased vaginal elasticity; increase in vaginal pH of over 5; and atrophy of the vulva, vagina, and urinary tract.[1,2] The array of associated examination findings and symptoms is referred to as genitourinary syndrome of menopause, of which vulvar and vaginal atrophy (VVA) is a major component.[3]

VVA is experienced to some extent by almost all postmenopausal women.[1] The most common symptoms are vaginal dryness, dyspareunia, itching, and irritation.[1,4,5] In contrast to vasomotor symptoms of menopause, which may abate over time, VVA symptoms tend to persist and may impact profoundly on sexual function, relationships, and quality of life. The quality-of-life impairment associated with moderate-to-severe VVA has been compared with that of chronic conditions such as arthritis, asthma, and irritable bowel syndrome.[6] Moreover, many postmenopausal women with or without VVA have age-related risk factors and comorbidities (e.g., obesity, increased cardiovascular risk, dyslipidemia, urinary incontinence, breast cancer, osteoporosis) that add to their overall disease burden. Nevertheless, VVA is a largely underdiagnosed and therefore undertreated condition. Many women view VVA symptoms as a natural part of aging, and may be reluctant or embarrassed to discuss their symptoms with a health practitioner.[3,4] Early diagnosis and adequate treatment of VVA are essential to maintain vaginal health, prevent progression, and avoid deterioration in quality of life.[3]

Local vaginal agents, such as lubricants and moisturizers, are common first-line treatments for mainly mild VVA. These products provide symptomatic relief, but do not treat the underlying condition, and are generally insufficient to manage more advanced cases. Moreover, many women find vaginal products inconvenient and messy to use.[4] Among postmenopausal women for whom VVA is the major complaint, vaginal estrogen therapy is one of the treatments of choice as it alleviates symptoms and restores vaginal health. However, many women are averse to, or poorly compliant with, local

administration or may not be candidates for estrogen therapy (e.g., because of a history of breast cancer).[2,3,7] Laser therapy improves vascularization of the vaginal mucosa, and may increase epithelial thickness,[3] but the durability of the therapeutic effect and safety of repeated applications are not yet clear.[8]

Selective estrogen receptor modulators (SERMs) are structurally diverse molecules that act by binding to estrogen receptors in hormone-responsive tissues.[9] SERMS display estrogenic or anti-estrogenic effects depending on the tissue.[9] Ospemifene is a third-generation SERM indicated for treatment of moderate-to-severe symptomatic VVA in postmenopausal women, who are not candidates for local vaginal estrogen therapy[10] or in whom estrogen products are contraindicated. Relative to other SERMs (e.g., tamoxifen, raloxifene, bazedoxifene), ospemifene has strong agonistic activity on vaginal tissues, antagonistic/inhibitory activity on breast tissue, and weak partial agonist/antagonist activity on endometrial tissue.[10,11] Ospemifene is administered orally, thus avoiding the inconveniences of local therapy. Ospemifene is the only therapeutic option approved for use in women with VVA and a history of breast cancer after all (including adjuvant) treatment has been completed.[12]

Meta-analyses have indicated that ospemifene significantly improves morphological and physiological features of the vaginal mucosa associated with postmenopausal VVA[13] and has a good safety profile.[14] The analyses examined six randomized controlled trials (RCTs) of ospemifene *versus* placebo involving 2086 women, who were followed for up to 52 weeks. Changes observed in vaginal pH, parabasal cells, superficial cells, and dyspareunia after 12 weeks' treatment were significantly in favor of ospemifene over placebo (all $p<0.0001$).[13] No differences were observed between ospemifene and placebo at 12 or 52 weeks in incidences of headaches, deep vein thrombosis, coronary heart disease, cardiovascular events, number of treatment discontinuations due to adverse events, or serious adverse events. A recently reported phase 3 clinical trial aligns with these findings.[15] At the 12-week evaluation, postmenopausal women with VVA treated with ospemifene (n=316) had significant improvements in percentages of parabasal and superficial cells, vaginal pH, and severity of vaginal dryness (all $p<0.0001$) compared with the placebo group (n=315). Between-group differences were statistically significant by week 4 of treatment.

As well as restoring vaginal health in postmenopausal women with symptomatic VVA, ospemifene may have other benefits of considerable importance to this population.

A significant positive effect for ospemifene relative to placebo on biochemical markers of bone turnover suggests a protective effect on bone health.[16]

Pooled data from 2166 postmenopausal women indicated that ospemifene 60 mg daily for up to 12 months improved some lipid parameters (decreased total cholesterol and low-density lipoprotein cholesterol; increased high-density lipoprotein cholesterol) compared with placebo suggesting a potential mitigation of the negative effects of menopause on the lipid profile, and showed no detrimental effect on coagulation parameters compared with placebo.[17]

Due to cancer treatments or risk-reducing strategies, VVA is more prevalent and may have an earlier onset in breast cancer survivors.[18] As systemic and local vaginal estrogen therapies are contraindicated in women with a history of breast cancer, other options to treat VVA are required. Animal models of breast cancer have shown that ospemifene inhibits tumor growth and is devoid of any stimulatory or estrogen agonist effects on breast tissue, possibly even imparting a chemoprotective effect.[19,20] During the ospemifene clinical trials program, accumulated breast safety data (i.e., treatment-emergent adverse events including cancer; mammogram and breast palpation findings) indicated no negative effects of active treatment on breast health.[21] A *post hoc* analysis of pooled data from three pivotal phase 3 studies found no differences in the efficacy or safety of ospemifene between women with a history of breast cancer (≥ 10 years prior to enrolment; n=11) and those without breast cancer (n=1091).[22] With regard to real-world use, an insurance claims database analysis from the USA found no difference in the breast cancer incidence rate between ospemifene-treated patients and similar untreated patients with VVA (1.3 *versus* 2.9 events per 1000 person-years).[23]

As reported in RCTs, ospemifene increased endometrial thickness compared with placebo, but the mean difference of <0.8 mm at any follow-up (12, 26 or 52 weeks) was not considered clinically relevant.[14] The incidence of vaginal bleeding at 12 or 52 weeks did not differ between ospemifene and placebo.[14] In phase 2/3 clinical trials of ospemifene for up to 1 year in postmenopausal women, no increase relative to placebo was observed in the incidence of endometrial hyperplasia or cancer or in the incidence of endometrial thickness ≥ 5 mm (2.6 *versus* 6.6%).[24]

Likewise, across all placebo-controlled clinical trials of ospemifene, the frequency of deep vein thrombosis events did not differ between active treatment and placebo: 3.65 *versus* 3.66 cases per 1000 patient-years.[10] Studies of ospemifene under real-world use identified no increase in the incidence of venous thromboembolism events among ospemifene-treated women *versus* untreated patients with VVA: 4 *versus* 12 events per 1000 person-years in the European Post-Approval Safety Study[25] and 3.7 *versus* 11.3 events per 1000 person-years in an insurance claims database analysis from the USA.[26]

In a pilot study, ospemifene was shown to normalize vestibular innervation sensitivity, possibly through an anti-neuroinflammatory activity, which may explain its efficacy against symptoms of vaginal burning and introital dyspareunia.[27]

Finally, although evidence is retrospective, and patient numbers were small, treatment with ospemifene for 12 weeks in postmenopausal women with VVA and overactive bladder syndrome was associated with a significant decrease in the number of voids, urgent micturition events, and nocturia events.[28]

The antagonistic activity of ospemifene in the breast, its neutral activity in the uterus, and its agonist activity in vagina and bone underlie its suitability for treating VVA. Non-hormonal treatment for VVA can address an unmet medical need in postmenopausal women by promoting vaginal health and providing several collateral benefits.[29]

To gain more insight into the profile of ospemifene in daily practice, the case studies presented in this Special Issue examine its use across a range of clinical scenarios in postmenopausal women with VVA. The case reports cover its effects on bone markers;[30] its use in breast cancer survivors[31] and in women with dyslipidemia,[32] urinary incontinence,[33] or VVA-related sexual dysfunction;[34] and its concomitant use with laser therapy.[35]

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