International Journal of Women's Health

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REVIEW

Ospemifene for Genitourinary Syndrome of Menopause: Patient Selection

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Abstract: Vulvar vaginal atrophy is a common condition affecting postmenopausal women, significantly impacting their quality of life. Fortunately, various treatment options are available, ranging from hormonal to non-hormonal therapies. Ospemifene has emerged as a promising non-hormonal alternative for managing vulvar vaginal atrophy. Its targeted approach, unique mechanism of action, favorable safety profile particularly for breast tissue, and efficacy make it a valuable option for women seeking relief from symptoms such as vaginal pain, dryness and dyspareunia and cannot receive estrogen supplementations. This is particularly the case for breast cancer survivors or women with a significant family history of estrogen-dependent cancers. Hence, tailored treatment plans, considering individual preferences and health circumstances, are essential in optimizing outcomes and improving the overall well-being of affected individuals.

Keywords: ospemifene, vulvovaginal atrophy, genitourinary syndrome of menopause, breast cancer, detrusor overactivity

Introduction

Physiological hypoestrogenism is responsible for the development of most climacteric symptoms related to menopause. Amongst the most bothersome is genitourinary syndrome of menopause (GSM), with symptoms such as dyspareunia, dysuria, vaginal dryness or pain and overactive bladder.[1,2] GSM has previously been called vulvar and vaginal atrophy (VVA), a common condition in postmenopausal women, characterized by thinning, drying, and inflammation of the vaginal walls and vulvar tissues due to decreased estrogen levels, triggering symptoms and impairing women's quality of life.[2]

Treatment options aim to alleviate these symptoms and improve the vaginal environment. There are several lines of management available that can be divided into two large groups: hormonal therapies (systemic or local estrogens) and non-hormonal therapies (selective estrogen receptor modulators (SERMs) like ospemifene, lubricants, long-acting vaginal moisturizers, or laser therapy). Local estrogen therapy is the first-line treatment for VVA due to its targeted effectiveness and tissue specificity in providing symptomatic relief as well as restoring vaginal tissue health.[3,4] It involves the application of vaginal estrogen in the form of topical cream, a tablet or ring. However, it is well known that some patients cannot receive estrogen therapy or are averse to or poorly compliant with its use. For these women in whom estrogen-therapy is contraindicated, such as those with a history of breast cancer[3,4] or those having localized adverse effects, then non-estrogenic therapeutic options such as ospemifene are a promising medication.

The other options such as vaginal moisturizers, vaginal lubricants and laser therapy are available as alternatives or adjuncts to treatment. Vaginal moisturizers are generally used for mild symptoms and are non-prescription, water-based vaginal preparations that can provide relief from vaginal dryness and discomfort.[3] Vaginal lubricants are used to reduce friction and discomfort during sexual intercourse. Unlike moisturizers, lubricants are typically used just before intercourse and can be water-based, silicone-based, or oil-based. Although both can help to alleviate VVA symptoms, they do not promote changes in the vaginal environment.[5] Fractional CO2 laser therapy or Erbium laser, also known as vaginal

Received: 3 February 2024
Accepted: 23 May 2024
Published: 5 June 2024

laser therapy, are a newer alternative treatment option. These involve the use of laser energy to stimulate collagen production, improve blood circulation, and rejuvenate vaginal tissues, reducing symptoms of VVA.[6]

The choice of treatment depends on factors such as the severity of symptoms, overall health, medical history, and personal preferences. Studies, however, show that ospemifene has been proven to increase the vaginal maturation index, improve vulvar vestibular symptoms and effective in normalizing vulvar vestibular innervation sensitivity,[7,8] contributing to it being a promising choice among the group of non-hormonal treatments.

Evidence of Benefit for Ospemifene

Ospemifene belongs to a class of drugs known as selective estrogen receptor modulators (SERMs). It binds to estrogen receptors in the vaginal epithelium, promoting the restoration of vaginal tissue integrity, by improving vaginal maturation index and vaginal pH,[9,10] and is indicated for moderate-to-severe VVA symptoms. Common side effects may include hot flushes, vaginal discharge, muscle spasms, and sweating.[11] It is metabolized by the liver, excreted in the bile, and eliminated in the feces in approximately 24 to 36 hours.[12] Being an oral medication negates the disadvantages of topical application.

Large, double-blind, placebo-controlled, randomized clinical trials have demonstrated safety and effectiveness of ospemifene in improving symptoms of dyspareunia and vaginal dryness compared to placebo in postmenopausal women. Also, ospemifene treatment has been shown to lead to a significant increase in the vaginal maturation index, indicating a positive effect on vaginal health and tissue integrity.[9,13–15] The ospemifene-mediated improvement of vulvar pain and dyspareunia is thought to be due to an attenuated sensitization of sensory nerves in the vestibular tissue, leading to an improved vestibular pallor, erythema, and moisture, and/or to a renewal and thickening of the vulvar epithelium.[7,8]

A multicenter, double-blind, phase 3 study randomized postmenopausal women with VVA and moderate-to-severe vaginal dryness as the most bothersome symptom to daily oral ospemifene 60 mg (n = 303) or placebo (n = 302). The efficacy of ospemifene was found to be significantly greater than that of placebo at week 12 for each of the following co-primary endpoints: percentages of parabasal and superficial cells, vaginal pH, and severity of dyspareunia. With ospemifene, the percentage of parabasal cells and vaginal pH significantly decreased; the percentage of superficial cells significantly increased; and dyspareunia was significantly reduced versus placebo (all $P < 0.0001$, except for dyspareunia: $P = 0.0001$).[9] A 12-week, double-blind, randomized phase 3 study conducted in 76 study centers in the United States randomized postmenopausal women to receive treatment with ospemifene 30mg/day (n = 282) or 60mg/day (n = 234) or placebo (n = 268). All women had 5% or less superficial cells on the vaginal smear (maturation index), vaginal pH greater than 5.0, and at least one moderate or severe symptom of vulvovaginal atrophy. The percentage of superficial cells was significantly increased in both the ospemifene 30 mg and 60 mg groups (7.8% and 10.8%, respectively) compared with the placebo group (2.2%; $P < 0.001$ for both). Significant improvements in maturation index were observed after 4 weeks of treatment ($P < 0.001$ for both ospemifene groups compared with the placebo group). The decrease in vaginal pH was 0.67 and 1.01 in the ospemifene 30 mg and 60 mg groups, respectively, compared with 0.10 in the placebo group ($P < 0.001$ for both). Vaginal dryness was significantly decreased in both the ospemifene 30 mg and 60mg groups (1.22 and 1.26, respectively) compared with the placebo group (0.84; $P = 0.04$).[14]

Another multicenter, double-blind phase 3 study randomized peri- and postmenopausal women (aged 40–80 years) with VVA and moderate-to-severe vaginal dryness as their most bothersome symptom to daily oral ospemifene 60mg (n = 316) or placebo (n = 315). They found that ospemifene significantly improved ($P < 0.0001$) the percentages of parabasal and superficial cells, vaginal pH, and severity of vaginal dryness compared with placebo at week 12. Secondary endpoints of dyspareunia ($P < 0.001$), maturation value index ($P < 0.0001$), and the Female Sexual Function Index ($P < 0.05$) also significantly improved with ospemifene versus placebo at 12 weeks. Significantly more women responded (31.5% vs 6.0%; $P < 0.0001$) or were satisfied (49.2% vs 33.8%; $P = 0.0007$) with ospemifene versus placebo at 12 weeks. The study concluded that ospemifene was effective and well tolerated.[15]

There are no direct comparison studies of ospemifene vs topical estrogen. However, a systematic indirect comparison of the two modalities showed no difference at 12 weeks for symptom scores when compared to placebo and better or comparable vaginal pH and vaginal maturation index improvements with ospemifene compared to topical estrogens.

There was no concerns regarding safety profile with either treatment. The authors concluded that the indirect comparison suggested that ospemifene had an efficacy, safety and tolerability profile equivalent if not better than topical oestrogens.[16]

Safety Profile

Longer-term studies have demonstrated the sustained benefits of ospemifene in managing VVA symptoms but also supporting its safety over extended periods of use.[17] It was not associated with clinically significant increases in endometrial thickness nor clinically relevant endometrial pathology. Network meta-analysis results showed that the post treatment endometrial thickness values (following 52 weeks of ospemifene use) were under the recognized clinical threshold value of 4 mm for significant risk of endometrial pathology. Endometrial thickness ranged between 2.1 and 2.3 mm at baseline and 2.5 and 3.2 mm after treatment.[18]

Placebo-controlled trials as well as real-life use of ospemifene have not shown an increase in venous thromboembolism among ospemifene using women when compared to non-ospemifene using women.[16,19]

Benefit on Lower Urinary Tract Symptoms

Overactive bladder symptoms, known to be part of GSM, have been shown to respond to ospemifene in earlier studies. Russo et al showed in an open-label trial of 40 women that cystometric capacity, bladder compliance and verbal sensory threshold responses during bladder filling on urodynamics were all improved after 12 weeks use of ospemifene ($P < 0.0001$). In addition, there was a reduction of number of daily voids, urge urinary incontinence episodes and nocturnal events in voiding diaries as well as improvement in International Consultation on Incontinence Questionnaire – Urinary Incontinence Short Form (ICIQ-UI SF) and International Consultation on Incontinence Questionnaire – Overactive Bladder (ICIQ-OAB) scores.[20] Similar findings were seen in another small study of 25 women with proven detrusor overactivity and VVA. After 12 weeks of 60mg Ospemifene, they observed a significant reduction in the number of voids in 24 hours, episodes of nocturia, urgency and incontinence, as well as an improvement in Overactive Bladder Questionnaire (OAB-Q) and Urogenital Distress Index 6 (UDI-6) Short Form questionnaires.[21] A retrospective analysis of 46 women with VVA treated with 60mg Ospemifene also demonstrated urodynamic improvement with a reduction in detrusor overactivity from 39% to 13% ($p = 0.04$), as well as bladder diary parameters and UDI-6 and OAB-Q score improvements.[22]

Ospemifene has also been trialed as a primary treatment for urgency symptoms in patients without vulvovaginal atrophy. Patients with mixed incontinence treated with a mid-urethral sling and ospemifene showed improvements in urodynamic and bladder diary parameters as well as quality of life questionnaires.[23]

Further Benefits

A significant positive effect from ospemifene compared to placebo on bone turnover biochemical markers suggests there is a protective effect on bone health.[24]

Pooled data from postmenopausal women (n = 2166) showed those taking ospemifene 60 mg daily for up to 12 months had improved lipid parameters compared with placebo suggesting a potential mitigation of the negative effects of menopause on the lipid profile. In addition, there was no detrimental effect on coagulation parameters compared with placebo.[25]

Specific Patient Groups

Estrogen-based therapies may not be suitable for all peri or postmenopausal women, particularly those with a personal or significant family history of estrogen-dependent cancers or those who are concerned about potential risks associated with estrogen use such as thromboembolic events and breast tenderness.[3] Due to the cancer treatments or risk-reducing strategies, VVA is therefore more prevalent and may have an earlier onset in breast cancer survivors.

Preclinical data, clinical data and systematic review have demonstrated ospemifene's antiestrogenic effect and its safety profile with regard to breast tissue, inhibiting tumor growth and possible chemoprotective effect.[17–19] Ospemifene is the only therapeutic option approved for use in women with VVA and a history of breast cancer.[26]

Conclusion

Treatment for VVA should be tailored to each woman based on factors such as their medical history, preferences, and overall health. Women should consult a healthcare provider to determine if ospemifene is an appropriate treatment option based on their specific circumstances. Healthcare providers should educate patients about the benefits and potential side effects of ospemifene to ensure informed decision-making. The National Institute for Care and Excellence (NICE) guidelines advise that if low-dose vaginal estrogens are not tolerated or contraindications in women with moderate-to-severe VVA symptoms, then a trial of oral ospemifene should be considered.[27] Being a non-hormonal treatment modality makes ospemifene an ideal option for women with a history of breast cancer or a strong family history of estrogen-dependent cancer.

Disclosure

Dr Dudley Robinson reports personal fees from Astellas, personal fees from AbbVie, personal fees from Pierre Fabre, during the conduct of the study. The authors report no other conflicts of interest in this work.

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