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CASE REPORT

Experience with ospemifene in patients with vulvovaginal atrophy treated with laser therapy: case studies

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Abstract

Vaginal laser therapy is a non-hormonal treatment option for vulvovaginal atrophy (VVA), a component of the genitourinary syndrome of menopause. Through a microablative and/or thermal effect on atrophic vaginal epithelium, laser therapy activates growth factors that increase vascularity and collagen production. Laser and ospemifene are complementary treatments: the laser's effects on intra- and extracellular water are supported by the activity of ospemifene at estrogen receptors to restore vaginal epithelium and natural lubrication. This article reports the clinical course of two women with dyspareunia preventing sexual intercourse who were treated with ospemifene and laser therapy. The woman in case 1 had extreme vaginal stenosis and severe VVA symptoms. CO_2 laser therapy accompanied by estriol vaginal gel and vaginal moisturizer was unsuccessful. After ospemifene and three sessions of laser therapy, followed by vaginal ring resection and continued physiotherapy-directed mechanical dilation of the vagina, she was asymptomatic within 6 months. The woman in case 2 had severe VVA, which had prevented penetration for 2 years. Ospemifene was administered for 1 month to prepare the vaginal epithelium for photothermal therapy. A single erbium:YAG laser session and continued ospemifene treatment improved her symptoms sufficiently to allow her to resume sexual relations within 2 months.

Keywords: laser therapy, ospemifene, vulvar and vaginal atrophy.

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Introduction

Approximately half of postmenopausal women experience vulvovaginal atrophy (VVA), a chronic and progressive condition arising from a hypoestrogenic state.[1] VVA is a major component of the genitourinary syndrome of menopause. As vaginal dryness and epithelial thinning contribute to pain and discomfort during intercourse, many women with VVA find sexual activity uncomfortable or impossible.[1]

Management of VVA includes the use of vaginal lubricants and moisturizers for temporary symptomatic relief and local estrogen therapy to revert the associated physiological changes.[2] The selective estrogen receptor modulator (SERM) ospemifene offers an alternative to hormonal therapy in women who are not candidates for vaginal estrogen therapy.[3] Ospemifene has agonistic activity in vaginal epithelium, antagonist activity in breast tissue, and neutral effects on the endometrium.[3] It is the first SERM to be approved for treatment of VVA, dyspareunia, and vaginal dryness.[4,5]

Another non-hormonal treatment for relief of VVA symptoms is vaginal laser therapy. Laser devices currently in use to treat VVA are the microablative fractional carbon dioxide (CO_2) laser and the non-ablative photothermal erbium:yttrium aluminum garnet (erbium:YAG) crystal laser. Laser waves act by heating connective tissue in the vaginal wall, thereby inducing collagen contraction, new collagen synthesis, vascularization, and growth factor infiltration. The net effect is increased thickness and restored elasticity and moisture of the vaginal mucosa.[6,7] Beneficial effects on VVA symptoms in postmenopausal women have been reported with the fractional CO_2 laser and erbium:YAG laser[8] and, recently, with the fractional CO_2 laser used concomitantly with ospemifene.[9] Laser therapy and ospemifene are complementary treatments for VVA: the laser's effects on the target chromophore (intra- and extracellular water)[10] are supported by the activity of ospemifene at

estrogen receptors to restore vaginal epithelium and natural lubrication.[3]

The case studies in this article report the experience of two postmenopausal women unable to maintain sexual activity due to severe dyspareunia who were treated with ospemifene and laser therapy. As patient-specific information was deidentified to ensure anonymity, patient consent was not required.

Case 1

Case 1 describes a 61-year-old woman (body mass index [BMI] 24.6 kg/m^2) who began menopause at 48 years. She presented VVA symptoms in July 2012 at age 53 years and developed vaginal stenosis at 56 years. Although sensitivity at the vestibular level was normal, on examination, she presented with pain in the vaginal canal in the region of the stenosis. She reported being unable to have sexual intercourse. Estriol vaginal gel was prescribed.

At presentation in July 2017, she had a new partner, and enquired about the possibility of resuming sexual relations. Physical examination revealed vaginal mucosa with few folds, petechiae, and severe dryness. A vaginal constriction ring was palpated at a depth of 4 cm with a central orifice of about 1 cm. The remaining approximate 4 cm of vaginal channel was measured using a cotton swab. On a 0–10 cm visual analog scale (VAS) to assess symptom intensity, she rated her dyspareunia and vaginal dryness as severe (both 10/10).

Three sessions of CO_2 laser therapy were administered at 4–6 week intervals, accompanied by estriol vaginal gel and vaginal moisturizer. At evaluation in October 2017, slight improvement in vaginal trophism was observed but narrowing was accentuated. A 3-cm channel was measured with a hysterometer and unidigital examination. Due to the substantial increase in vaginal narrowing with loss of both amplitude and diameter of the canal, and her inability to have sexual intercourse despite treatment, a concentric vaginal ring resection was scheduled.

Vaginal ring resection was performed in November 2017 and the postoperative recovery was normal, but it was not possible to measure the patient's intravaginal diameter to an adequate depth by bidigital evaluation. She was instructed to use a vaginal dilator starting at 20 mm diameter, along with local estrogen therapy and vaginal moisturizer for 6 weeks.

The following week, the patient returned to the clinic asking to discontinue treatment due to lack of improvement and need for daily moisturizing. She was unable to insert the estradiol vaginal ring because of vaginal narrowing. Following a discussion of options, a decision was taken to begin treatment with ospemifene 60 mg daily and fractional CO_2 laser (dot power 40 W, dwell time 1000 µs, dot spacing 1000 µm).

At the first laser session in December 2017, the probe could not be introduced beyond the external one-third of the vaginal canal. Ospemifene was maintained, and physiotherapy (mechanical stimulation under supervision) for muscle rigidity was introduced.

The patient began to show signs of clinical improvement and was able to introduce dilators of greater diameter (up to 35 mm). In two successive sessions of CO_2 laser therapy performed at 4-weekly intervals, the probe could be introduced to the middle of the vaginal canal (approximately 5 cm) without difficulty.

In February 2018, the patient attended the clinic reporting the sensation of a short vagina. A gynecological examination revealed normal vaginal trophism with good elasticity, turgor, visible folds, and a vaginal length of approximately 5 cm by (painless) bidigital examination. A rigid fibrotic vaginal ring persisted in the middle third of the vagina through which the cervix could be visualized. The patient agreed to surgical resection of the vaginal ring, which was performed in April 2018 without complications. In the immediate postoperative period, a 40-mm dilator could be placed to about 7 cm of the vaginal length and was used as a mechanical stimulus for the next 4 weeks under supervision of the physiotherapy team. Additional treatment consisted of ospemifene, vaginal moisturizer, and pelvic floor rehabilitation.

At a clinic visit in June 2018, the patient was asymptomatic and able to maintain sexual relations without difficulty. A gynecological examination confirmed normal vaginal trophism. Bidigital evaluation and vaginal speculum placement were performed without difficulty, perineal muscle tone was normal, and the cervix was visible. Dyspareunia and vaginal dryness were markedly improved, with VAS scores of 4 (mild) for each.

The case was discussed in a clinical session to gain a possible consensus about continuing ospemifene treatment to prevent reversion to severe atrophy and formation of new restrictive vaginal rings. Despite the patient's needs and preferences, it was decided to continue CO_2 laser therapy as ospemifene is currently indicated for treatment, not prevention, of moderate-to-severe vaginal atrophy.

Treatment continued with vaginal gel moisturizer. A laser CO_2 phototherapy memory session was performed in February 2019, at which time the patient was asymptomatic and reported no difficulty with sexual relations.

Case 2

Case 2 involves a 63-year-old woman (BMI 25.7 kg/m^2) with a gynecological history of three pregnancies (one vaginal delivery, two abortions) and no gynecological surgeries. She entered menopause at age 45 years without requirement for menopausal hormone therapy. She is a non-smoker and exercises regularly (swimming and paddle tennis). Comorbidities were hypothyroidism (treated with levothyroxine 75 mcg), atopic dermatitis, and penicillin allergy.

During the 10 years prior to her presentation in October 2018, the patient had experienced vulvovaginal itching, stinging, and pain at the start of sexual intercourse. In the previous 2 years, penetration had become impossible and stretch-type wounds were present in the vaginal vestibule. Vaginal cytology from 2 years earlier (her regular gynecologist) showed an atrophic

smear with absence of endocervical cells. Treatment with a local hyaluronic acid-based vulvovaginal moisturizer was recommended.

During examination, the patient mentioned occasional use of corticosteroid cream (clobetasol propionate), as previously prescribed, for intense itching. She denied stress- or urge-related urinary incontinence, but reported occasional nocturia depending on her fluid intake in the afternoon/evening, which she managed by using a pantyliner at night. A range of blood tests (requested by her endocrinologist and performed 2 months before the consultation) indicated that her thyroid, lipid, and glucose levels, coagulation factors, and liver function were within normal ranges.

Gynecological examination revealed severe atrophy of the external genitalia in the form of pale and friable epithelial tissue, atrophic (almost absent) minor labia, and significant lipodystrophy in the major labia. The vagina was pale with loss of rugae. She reported pain on examination (VAS score of 8/10) and an intense burning sensation, which prevented contact with the vaginal vestibule where two superficial wounds were visible. A vaginal speculum was inserted to perform cervical–vaginal cytology. Results indicated severe atrophy, absence of endocervical cells, and presence of parabasal cells. Vaginal pH was 7 and the Vaginal Health Index score was 4/25. A urine culture was requested for assessment at a subsequent consultation.

Based on the degree of clinical atrophy and epithelial bleeding after vulvovaginal manipulation, ospemifene 60 mg daily for 1 month was prescribed to prepare the epithelium for photothermal therapy. At re-evaluation 30 days later, the patient reported no stinging sensation, and no discomfort when wearing underwear, although she remained fearful about attempting sexual intercourse. The urine culture was negative.

In December 2018, a gynecological examination showed improvement in vaginal color. The vaginal epithelium was moist and more elastic, and vestibular lesions were absent. Improvements were recorded in vaginal pH (5.5), VAS scores for dyspareunia (6/10) and dryness (6/10), and Vaginal Health Index score (12/25). In discussion with the patient, it was decided to combine ospemifene with vaginal photothermal laser therapy (erbium:YAG).

The procedure was performed according to the parameters of the laser's phase 1 program: spot size (diameter of laser beam on target) 7 mm; pulse frequency 1.6 Hz; and fluence (laser energy delivered per unit area) 5.5 J/cm^2. Briefly, after inserting a purpose-designed speculum into the vagina, the probe is inserted into the speculum without direct contact with the vaginal mucosa. Circular irradiation of the vaginal wall is carried out, with 4 pulses delivered every 5 mm. The probe is retracted each time (using the graduated scale on the probe) until it reaches the entrance of the vaginal canal. The procedure is repeated three times by rotating the speculum 45° to cover the entire surface of vaginal tissue. For the second treatment step, the speculum is removed and the probe is changed. The vestibule and introitus vaginae are irradiated according to the parameters of the laser's phase 2 program: spot size 7 mm; pulse frequency 1.6 Hz; and fluence 10 J/cm^2. Patients are advised to avoid sexual intercourse for 3–7 days after treatment. The protocol typically consists of three laser applications every 30 days, with follow-up visits at 4, 12, and 24 weeks after the last application.[11] Based on symptom evaluation using VAS and Vaginal Health Index scores, the need for a 'memory session' is decided in consultation with the patient.

At follow-up after one laser application and 60 days' ospemifene treatment, the patient reported no vaginal itching or stinging, and more comfortable vaginal penetration during sexual intercourse. She no longer required vaginal moisturizers or a night-time pantyliner. Laser application was not repeated in the second month and the patient was schedule for re-evaluation in 30 days.

At follow-up after one laser application and 90 days' ospemifene treatment, further improvement was observed. Vaginal color was better, the epithelium was moist and more elastic, and vestibular lesions were absent. Vaginal pH was 3.5, VAS scores for dyspareunia and dryness were both 3/10, and the Vaginal Health Index score was 16/25. The patient was sexually active without discomfort. Ospemifene was maintained until 6 months.

At follow-up after one laser application and 6 months' ospemifene treatment, improvements were maintained in vaginal color, moisture and elasticity of the vaginal epithelium, and absence of vestibular lesions. Vaginal pH was 4, VAS scores for dyspareunia and dryness were both 2/10, and the Vaginal Health Index score remained at 16/25. The patient reported more frequent and satisfying sexual intercourse. We performed a laser therapy memory session consisting of two (not three) repetitions of each phase of the protocol. Oral ospemifene was discontinued.

At follow-up 6 weeks later, gynecological improvements were maintained. The patient was scheduled for follow-up every 90 days for up to 1 year and was advised to use lubricants as required for sexual intercourse.

Clinical overview

Vaginal laser therapy is a new approach to manage VVA symptoms in postmenopausal women. Through a thermal effect on atrophic vaginal epithelium, laser therapy activates growth factors that increase vascularity and collagen production, and thickens the epithelium by forming new papilla.[12] As the effect of laser therapy depends on the water content of target tissue, any treatment that improves trophism, and therefore the tissue's own degree of hydration, might be expected to enhance its effect, providing a rationale for combined use with vaginal estrogen or ospemifene.

Evidence has been reviewed for the efficacy and safety of the fractional CO_2 laser (23 case series, one randomized controlled trial [RCT], n=1179) and erbium:YAG laser (11 case series; n=692) in the treatment of VVA.[8] All studies were single center and none included a genuine placebo group.

The authors concluded that the techniques appear to be safe with results persisting for up to 12 months, but highlighted the need for larger well-controlled studies.[8] In the single RCT performed to date, the efficacy of fractional CO_2 laser, topical estriol, and combined (i.e., laser + estriol) treatment was compared in 45 postmenopausal women with VVA.[13] Based on VAS scores for dyspareunia, dryness, and burning, Vaginal Health Index scores, and Female Sexual Function Index scores, the authors concluded that CO_2 laser alone or in combination with topical estriol is a 'good treatment option for VVA symptoms',[13] although the conclusions were questioned due to methodological shortcomings and disparity between the reported results.[14] The United States Food & Drug Administration currently warns against the use of lasers to treat vaginal symptoms and/or conditions on the basis that the "safety and effectiveness of energy-based devices for treatment of these conditions has not been established."[15]

An interesting retrospective study from a single center in Italy analyzed outcomes in 72 women with VVA who were treated with three monthly sessions of CO_2 laser therapy and had 3-month follow-up data.[9] Among the cohort were 39 women treated concomitantly with CO_2 laser and ospemifene 60 mg daily. At 3-month follow-up, symptoms were reduced significantly in both groups (laser alone; laser + ospemifene), but relief of vaginal dryness and dyspareunia was more pronounced in the laser + ospemifene group suggesting added benefit. Significant improvement *versus* baseline in the vestibular health score was apparent in the laser + ospemifene group within 4 weeks of the first laser session.

Both case studies in this article featured women with vaginal symptoms preventing sexual intercourse. Case 1 was complicated by extreme vaginal stenosis in addition to severe VVA. CO_2 laser therapy and estriol vaginal gel had failed to provide improvement. Although no clinical literature was available at the time (2017–2018) about concomitant use of CO_2 laser therapy and ospemifene, individually each has shown efficacy similar to that of estrogen in the treatment of VVA. At our initial attempt to perform laser phototherapy, we were unable to insert the vaginal probe. After continued treatment with ospemifene, we could introduce the vaginal probe and perform the laser sessions. We attribute improvement in the patient's vaginal health to ospemifene and associated recovery to trophism. A second surgical vaginal ring resection was performed and treatment continued with mechanical stimulus, ospemifene, vaginal moisturizer, and pelvic floor rehabilitation, eventually allowing the patient to resume sexual activity within 6 months. Case 2 involved a woman with a 2-year history of dyspareunia preventing penetration. In this case, ospemifene 60 mg/day for 1 month was used to prepare and condition her vaginal epithelium for erbium:YAG laser therapy. The rationale is that ospemifene improves microvascularization and, in turn, hydration of the urogenital epithelium. The vaginal laser acts as an energy source (chromophore action), initially capturing water from the newly created hydration and, secondly, stimulating production of collagen and elastin in the epithelium. In our experience, this preparatory step reduces discomfort, improves clinical and cytological outcomes, and is supported by Doppler flow study of the vaginal wall showing increased angiogenesis. After just one laser session and 60 days' treatment with ospemifene, she was able to resume sexual relations. Our experience suggests that combined ospemifene + laser therapy has the potential to reduce the number of laser sessions required, which can alleviate treatment burden and possibly introduce cost-savings for the patient and healthcare system. Another potential benefit is to prolong clinical and subclinical improvement in vaginal tissues, although this must be demonstrated in controlled studies.

Conclusions

Postmenopausal women with VVA and severe dyspareunia can benefit from combined treatment with laser therapy and ospemifene. As shown in the case studies, ospemifene appears to be useful in preparing and conditioning the vaginal epithelium for laser therapy, at minimum allowing laser therapy to be performed and potentially augmenting its beneficial effects.

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References

1. Mac Bride MB, Rhodes DJ, Shuster LT. Vulvovaginal atrophy. *Mayo Clin Proc*. 2010;85(1):87–94. https://doi.org/10.1089/jwh.2012.3969
2. Palacios S, Cancelo MJ. Clinical update on the use of ospemifene in the treatment of severe symptomatic vulvar and vaginal atrophy. *Int J Womens Health*. 2016;8:617–626. https://doi.org/10.2147/IJWH.S110035
3. Kangas L, Unkila M. Tissue selectivity of ospemifene: pharmacologic profile and clinical implications. *Steroids*. 2013;78:1273–1280. https://doi.org/10.1016/j.steroids.2013.09.003
4. Senshio®. Summary of product characteristics. Available at: https://www.medicines.org.uk/emc/product/9417/smpc. Accessed November 14, 2019.
5. Osphena (ospemifene). Prescribing information 2019. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/203505s015lbl.pdf. Accessed February 14, 2020.
6. Gandhi J, Chen A, Dagur G, et al. Genitourinary syndrome of menopause: an overview of clinical manifestations, pathophysiology, etiology, evaluation, and management. *Am J Obstet Gynecol*. 2016;215(6):704–711. https://doi.org/10.1016/j.ajog.2016.07.045
7. Alvisi S, Gava G, Orsili I, et al. Vaginal health in menopausal women. *Medicina (Kaunas)*. 2019;55(10). https://doi.org/10.3390/medicina55100615
8. Photiou L, Lin MJ, Dubin DP, et al. Review of non-invasive vulvovaginal rejuvenation. *J Eur Acad Dermatol Venereol*. 2020;34(4): 716–726. https://doi.org/10.1111/jdv.16066
9. Murina F, Felice R, Di Francesco S, et al. Ospemifene plus fractional CO_2 laser: a powerful strategy to treat postmenopausal vulvar pain. *Gynecol Endocrinol*. 2019;1–5. https://doi.org/10.1080/09513590.2019.1680625
10. Omi T, Numano K. The role of the CO_2 laser and fractional CO_2 laser in dermatology. *Laser Ther*. 2014;23(1):49–60. https://doi.org/10.5978/islsm.14-RE-01
11. Gambacciani M, Levancini M, Cervigni M. Vaginal erbium laser: the second-generation thermotherapy for the genitourinary syndrome of menopause. *Climacteric*. 2015;18(5):757–763. https://doi.org/10.3109/13697137.2015.1045485
12. Salvatore S, Athanasiou S, Candiani M. The use of pulsed CO_2 lasers for the treatment of vulvovaginal atrophy. *Curr Opin Obstet Gynecol*. 2015;27(6):504–508. https://doi.org/10.1097/GCO.0000000000000230
13. Cruz VL, Steiner ML, Pompei LM, et al. Randomized, double-blind, placebo-controlled clinical trial for evaluating the efficacy of fractional CO_2 laser compared with topical estriol in the treatment of vaginal atrophy in postmenopausal women. *Menopause*. 2018;25(1):21–28. https://doi.org/10.1097/GME.0000000000000955
14. Buttini MJ, Maher C. The first published randomised controlled trial of laser treatment for vaginal atrophy raises serious questions. *Med J Aust*. 2018;209(9):376–377. https://doi.org/10.5694/mja18.00187
15. U.S. Food & Drug Administration. FDA warns against use of energy-based devices to perform vaginal 'rejuvenation' or vaginal cosmetic procedures: FDA Safety Communication. Available at: https://www.fda.gov/medical-devices/safety-communications/fda-warns-against-use-energy-based-devices-perform-vaginal-rejuvenation-or-vaginal-cosmetic. Accessed February 20, 2020.